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COVER PHOTO PICTURE

A hospital scene shows a young child receiving treatment for leukemia. A child, bald from the treatment, sits in a hospital bed, surrounded by his family. The illustration is done according to the paper by Roganović et al., "Late Adverse Effects after Treatment for Childhood Acute Leukemia, published in this issue of the journal". Cover page generated and supported by (DALL·E image generation).

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Instructions to authors can be found at http://www.ama.ba/forms/20220520_AMA-Instructions%20to%20authors.pdf. Home page of the Journal www.ama.ba offers free access to all articles.

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Difficulties in Accessing the List and Full Text of the Defended PhD Theses from Medical Schools: a Retrospective Case Study from Croatia

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Abstract

Objective. To conduct scientometric studies on PhD ("Doctor of Philosophy") theses (i.e., doctoral theses), researchers should be able to access the theses. We aimed to explore how to obtain a list and full text of the defended PhD theses from medical schools in Croatia over 30 years (from the beginning of 1992 to the end of 2021). **Methods.** We tried to obtain information from the Croatian Bureau of Statistics, the National and University Library in Zagreb (NSK), universities, medical schools and online repositories. **Results.** We could not find a single list (source) of all PhD theses. Based on 4 different sources (website of the University of Zagreb and Medical School in Rijeka; school administrator from Split; library catalog from Osijek), we gathered information that from the beginning of 1992 to the end of 2021, there were 2955 PhD theses defended at medical schools in Croatia – 357 in Osijek, 550 in Rijeka, 337 in Split and 1711 in Zagreb. In May 2022, the online Croatian Digital Dissertations Repository contained 631 (22%) of full-text theses in Portable Document Format (PDF). University of Zagreb School of Medicine has its own repository that holds the full text of 834 (49%) of their PhD theses. One of the three PhD programs of the University of Split School of Medicine, namely Translational Research in Biomedicine (TRIBE), published full texts of all PhD theses defended at that program on its website. NSK held 2650 (90%) of the theses in a printed version. **Conclusion.** It was extremely challenging to access the list and full texts of doctoral theses defended in Croatia. Making PhD theses publicly available would ensure transparency and enable analyses that should improve scientific policy.

Key Words: Theses ▪ PhD ▪ Doctorates ▪ Medical Education ▪ Scientometrics.

Introduction

Completion rates and time-to-degree of PhD ("Doctor of Philosophy") programs (i.e., doctoral programs) are crucial metrics for tracking the supply and demand of researchers in the academic labor market and assessing the efficacy and efficiency of PhD education (1-3). High attrition, low completion rates, and a lengthy time-to-degree have a detrimental impact on the return on investment in PhD education (4), from a cost-effective economic point of view of funders, institutions, and supervisors and an effective career path perspective of a student (5). Time-to-degree and completion rates have been the conventional metrics for evaluating the effectiveness of PhD education programs. However, it is difficult to find data on the topic, particularly for European PhD programs, because such information is rarely disclosed, whether at the institutional, discipline, or national level (6).

Beyond analyses of PhD completion rates, time to degree, and factors influencing them (6, 7), the PhD theses can be the subject of various scientific analyses. Examples of such studies include assessing the PhD thesis' quality of writing (8), bibliometric profile (9), research methodology (10), publication output, article/journal impact of the manuscripts published from the theses (11), and theses submission rules (12, 13), among other topics.

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However, to conduct any studies on PhD theses, researchers should have easy access to the list of defended theses from the targeted institution(s) and access to the full text of the thesis. In 1991, Breimer and Mikhailidis proposed that PhD theses should be made publically and easily available [quote]: "to allow audience participation, the theses must be freely available to the scientific community" (14). Breimer and Mikhailidis proposed that a free International Thesis Journal should be established (14). In 1989, a British scientist, Tim Berners-Lee, invented the World Wide Web (WWW), while working at the European Organization for Nuclear Research (CERN). On 30 April 1993, CERN made the source code of WWW available on a royalty-free basis, making it free software and thus creating the world's first web browser and editor. This emerging information network developed into the Internet as we know it today (15). In 1995, Lars H. Breimer and Douwe D. Breimer observed that doctoral theses represent a largely inaccessible mine of useful information and suggested that doctoral theses should be made freely available through the Internet (16). One would expect that nowadays, all PhD theses would be easily retrievable online.

As researchers, we were interested in conducting bibliometric studies on biomedical PhD theses defended in medical schools in Croatia. However, we were not aware of whether there are repositories or similar sources where one could easily find a full list and full texts of such PhD theses.

In this study, we aimed to explore how to obtain a list and full text of the defended PhD theses from medical schools in Croatia.

Methods

Study Design

This was a retrospective study.

Ethics

The study protocol was approved by the Ethics Committee of the University of Split School of Medicine. The study was conducted in line with all the applicable ethical codes and laws.

Data Collected

We searched for a list and full texts of defended PhD theses in medical schools in Croatia (in Osijek, Rijeka, Split, and Zagreb) over 30 years (from the beginning of 1992 to the end of 2021).

Information Sources

To obtain the list of targeted PhD theses, we contacted the Croatian Bureau of Statistics, the National and University Library in Zagreb, universities and medical schools. To access full texts of defended PhD theses, we searched the online Croatian Digital Dissertations Repository (https://dr.nsk.hr/en; last accessed February 12, 2024) of the National and University Library in Zagreb (NSK), which publishes Master of Science (MSc) and PhD theses uploaded by institutions. The Repository has the English version of the website and various search functionalities, including the option to search for the type of thesis (MSc vs PhD thesis), search per author, per institution, etc. We also analyzed the websites of universities and medical schools. The search for information was conducted from May to December of 2022.

The Croatian Bureau of Statistics Does Not Share Any Data due to Personal Data Protection

The first logical place to look for information about the defended PhD theses was the Croatian Bureau of Statistics because each student completing any kind of thesis needs to fill out a detailed statistical form that needs to be sent to the Bureau. The information available on the website of the Croatian Bureau of Statistics was not helpful for our aim. Namely, the Croatian Bureau of Statistics publishes annually on its website the number of PhD students enrolled in each school and an aggregate number of defended PhD theses for each university. The Bureau's decision to publish just the number of enrolled students per school and the number of defended PhD theses per university prevents any estimates about the PhD completion rates of individual schools. When we contacted the

Croatian Bureau of Statistics via email to ask for data, they responded that they are unable to share any data about defended theses with us due to personal data protection issues, i.e., GDPR (General Data Protection Regulation).

National and University Library in Zagreb Does Not Have All Phd Theses Defended in Croatia

NSK is the national bibliographic center of Croatia, and when students defend their PhD thesis, they used to be obliged to print one copy to be sent to the NSK. However, by searching the NSK catalogue (https://katalog.nsk.hr/F?RN=233152322; last accessed February 12, 2024) we were unable to retrieve the information we were looking for. Namely, their catalog does not allow user-friendly search for PhD theses. There is a drop-down menu available in the online search of the NSK catalogue, but it does not offer any type of thesis to be chosen as an information source. When contacted via e-mail, NSK responded that they do not have a systematized list of all defended theses in medical schools in Croatia. They also indicated that they could not guarantee that their catalog of PhD theses contains all PhD theses defended because the institutions were legally obliged to deliver one copy of a PhD thesis to the NSK only from 2013. They indicated that the most complete and relevant results should be obtained from universities and schools themselves. When we asked NSK to export for us the list of the PhD theses that they have received from medical schools, we received information that this is a paid service that costs 13.20 EUR per hour, but that they can send us instructions on how to search their catalog by ourselves. One of the authors (MT) went personally to the NSK to be trained in searching their online catalog.

We considered analyzing PhD theses stored as printed copies in the NSK. The information on the NSK website indicated that a maximum of 10 records could be borrowed to be studied at once, and for each one, the reader needs to fill out the request form. This means that it would be an extremely burdensome and long-term process to try to analyze full texts of theses deposited in NSK if one can borrow only 10 theses per day and fill out a paper form for each of the thesis analyzed.

Searching Institutional Websites

Institutional websites of the School of Medicine in Osijek published a series of Portable Document Format (PDF) files for each academic year from 2010/2011 onwards (https://www.mefos.unios.hr/index.php/hr/doktorski-radovi-u-postupku; last accessed February 12, 2024). For each defended thesis, the list includes the name of the PhD holder, date of defense, thesis title and the name of the mentor. Medical School in Rijeka publishes a list of defended PhD theses divided into sections per decade and years (https://medri.uniri.hr/znanost/obranjeni-doktorati/; last accessed February 12, 2024). The information provided includes the name of the PhD holder, date of defense and thesis title. However, the website did not allow for a simple download of the information.

At the time when the study was conducted, the University of Split School of Medicine had three PhD programs, whereas each published a full or partial list of defended PhD theses. Those programs were: Biology of Neoplasms (https://mefst.unist.hr/studiji/doktorska-skola/biologija-novotvorina/bn-doktorati/4833), Evidence-Based Medicine (https://mefst.unist.hr/studiji/doktorska-skola/ebm-98/ebm-doktorati/4791) and Translational Research in Biomedicine – TRIBE (https://mefst.unist.hr/studies/graduate-school/tribe/defended-theses/1812). All three websites were last accessed on February 12, 2024. For each thesis, those websites publish information about the name of the PhD holder, date of defense, thesis title, name of the mentor, and list of published articles that were published to qualify for thesis defense.

The University of Split School of Medicine contained only a partial list of defended PhD theses on their website. The School currently has three PhD programs. One of the programs, namely Translational Research in Biomedicine (TRIBE), contained the full list of PhD theses defended in that program. The other two PhD programs

contained a partial list of PhD theses defended at those programs. Furthermore, the University of Split School of Medicine has had in the past another PhD program, which was closed in the meantime, and some students defended their PhD theses based on publications, without the need to enroll in the PhD program at the University of Split School of Medicine. Thus, even if all three current PhD programs at the University of Split School of Medicine had published on their website a full list of defended PhD theses, that list would not be complete for that School.

When we contacted the administrator of the Postgraduate Education office to obtain the full list of the PhD theses defended at the School, the administrator would only release the list with the permission of the Ethics Committee. Thus, we submitted the study protocol to the Ethics Committee of the University of Split School of Medicine and received its approval.

Subsequently, the administrator from the Postgraduate Education office provided a list of doctoral theses, which contained a full list of PhD holder names, but with a partial list of mentors and without the names of the defended theses.

When the study was conducted, the University of Zagreb had a searchable list of PhD theses defended at the entire university on its website (https://www.unizg.hr/istrazivanje/doktorski-studiji/promocija-doktora-znanosti/promovirani-na-sveucilistu-u-zagrebu-pretrazivanje/). This web site was last accessed on May 7, 2022. That website contained a full list of PhD theses defended at all schools of that university. However, that list did not allow for the filtering of theses defended per school. Thus, we first had to retrieve the full list of all PhD theses of the University of Zagreb, and then filter those belonging to the University of Zagreb School of Medicine.

However, at the time of the manuscript writing, that searchable database was no longer available. The only available information that remained on the University of Zagreb website were PDF files listing "books" with the list of PhD theses that were promoted at the University convocation ceremonies (https://www.unizg.hr/istrazivanje/doktorski-studiji/promocija-doktora-znanosti/knjige-doktora-znanosti/). Those "books" contain the following information for each defended PhD theses: a photograph of the PhD holder, name of the PhD holder, thesis title, language of the thesis, research area, short CV of the PhD holder, School name, mentor's name, names of the thesis defense committee, date of defense, a summary of the thesis in the Croatian language and in the English language.

We also explored the University of Zagreb School of Medicine's institutional online repository (http://medlib.mef.hr/; last accessed February 12, 2024) to see how many full-text theses can be found there. This Repository can be searched in the English language. There is an option to search for a thesis among the literature types; however, it does not allow searching based on the thesis type (http://medlib.mef.hr/cgi/search/advanced; last accessed February 12, 2024).

Data Analysis

Descriptive statistics was conducted and data were shown as frequencies and percentages.

Raw Data

All raw data collected within the study are available on Open Science Framework (link: https://osf.io/hz52g/).

Results

A Single List of Defended Phd Theses in Croatia Does Not Exist

We were unable to find a single source of information about PhD theses defended in all four Croatian medical schools, neither at the Croatian Bureau of Statistics nor NSK. We had to search multiple information sources to obtain the list of PhD theses (Table 1).

Table 1. Results of Searching Various Information Sources for the List and Full Text of PhD Theses Defended at Medical Schools in Croatia from the Beginning of 1992 to the End of 2021

Information source	Number of PhD theses found via this source	Availability of full-text theses
Croatian Bureau of Statistics	0	Full-text of theses not available in this source
National and University Library in Zagreb (NSK)	2650 theses from all four targeted medical schools (90% of all defended theses)	Paper copies available in the NSK; one can borrow a maximum of 10 thesis per day
Croatian Digital Dissertations Repository	631 theses from all four targeted medical schools (21% of al defended theses)	Portable Document File (PDF) version of the theses available in the repository
Medical School in Osijek website	308 theses defended at Medical School in Osijek from 2010 onwards (86% of theses defended at that School)	Full-text of theses not available on the website
Medical School in Osijek Library Catalogue	232 theses defended before 2015 (65% of theses defended at that School)	Paper copies available in the School Library
Medical School in Rijeka website	550 (all theses defended at Medical School in Rijeka)	Paper copies available in the School Library
University of Split School of Medicine Postgraduate Office	337 (all theses defended at the University of Split School of Medicine)	Paper copies available in the School Library
University of Zagreb website	1711 (all theses defended at the University of Zagreb School of Medicine)	Paper copies available in the School Library
University of Zagreb School of Medicine online repository	834 theses defended at the University of Zagreb School of Medicine (49% of theses defended at that school)	PDF version of the theses available in the repository

National and University Library in Zagreb

Upon training, our search indicated that NSK has 4616 records for PhD and MSc theses from medical schools in Croatia in their catalog. Some of those records are printed versions of PhD theses, and some records denote CDs containing theses. The catalog lists 2650 printed PhD theses from medical schools in Croatia in the targeted period (from the beginning of 1992 to the end of 2021).

Medical School in Osijek Published a Partial List of Defended Phd Theses on Its Website

Medical School in Osijek published most PhD theses defended from 2015 onwards in their online repositories. On the School's website, a list of PhD theses published from 2010 onwards was published, and this list includes 308 PhD theses. We manually searched the School's library catalog to extract data about the PhD theses of that school that were deposited in the library before 2015. There were 232 PhD theses in the library catalog that were defended before 2015. By considering all these sources of information, we concluded that 357 PhD theses were defended at the Medical School in Osijek during the targeted period.

Medical School in Rijeka Published a Full List of Defended Phd Theses on Its Website

Medical School in Rijeka has a commendable website as it contains the full list of PhD theses defended at that school, from the school's inception to the present time. There were 550 PhD theses defended at the Medical School in Rijeka during the targeted period.

University of Split School of Medicine Published a Partial List of Defended Phd Theses on Its Website

Since the University of Split School of Medicine published a partial list of defended PhD theses on its website, we obtained the full list of defended theses from the administrator of the Postgraduate Education office. There were 337 PhD theses defended at the University of Split School of Medicine during the targeted period. Upon multiple reminders, we got

the complete information about the doctoral theses defended only at one PhD program.

University of Zagreb Had a Downloadable List of Theses

By filtering offline downloaded theses from the searchable database of the University of Zagreb, we isolated the number of 1711 PhD theses defended at the Medical School in Zagreb during the targeted period.

Medical School in Zagreb Has a Partial Online Repository

The online repository of the University of Zagreb School of Medicine held PDFs of 834 theses, all defended between 2003 and 2020 (49% of their PhD theses defended between 1992 and 2021).

Using Multiple Sources to Get to the List and Number of Theses Defended

Finally, based on the information from the website of the University of Zagreb, the website of the Medical School in Rijeka, the administrator from the University of Split School of Medicine and the library catalog of the Medical School in Osijek, we concluded that from the beginning of the 1992 to the end of 2021, there were 2955 PhD theses defended at medical schools in Croatia – 357 in Osijek, 550 in Rijeka, 337 in Split and 1711 in Zagreb.

The Online Phd Theses Repository Contains Only 22% of the Targeted Theses

The online Croatian Digital Dissertations Repository contained 631 (21%) theses defended at medical schools in Croatia from 1992-2021.

NSK Holds 94% of the Targeted Theses

The most complete source of targeted theses was NSK, which held 2650 (90%) of all theses.

Discussion

Our case study shows that accessing the list and full texts of PhD theses defended in medical schools in Croatia is very challenging. Using four different sources of information, we came to the number of 2955 PhD theses defended at medical schools in Croatia from 1992 to 2021. However, only one of the Schools had the list of all defended PhD theses available on its website. For the remaining three schools, laborious methods had to be employed to access the list of defended theses, sometimes with partial information. The national online repository of Doctoral and MSc theses contained only 21% of all the targeted theses. Thus, accessing the majority of those theses would involve visiting school or NSK libraries and using laborious manual searching of the theses. It has been posited that academic theses must be publicly accessible for scientific, economic, and ethical reasons (14, 16, 17). Open access (OA) publication of defended theses online has multiple benefits.

Ferreras-Fernández et al. have shown that the OA publication of theses increases their visibility and use and also produces a significant citation rate (18). This is also important for transparency and the prevention of plagiarism. The case study of Ocholla showed that plagiarism could be significantly reduced in academic theses if students were aware that text similarity would be used to verify their work and if they knew that their work would appear on an online OA space/platform (19). The current situation in Croatia with accessing the list of defended PhD theses in medical schools between 1992 and 2021 is troubling.

It is concerning that there is not a single list on the national level of the PhD theses defended and that obtaining this information required so many sources and effort. In October 2022, a new law, the *Scientific Activity and Higher Education Act,* was adopted in Croatia. According to this law, "The holder of the doctoral study is obliged to publish the doctoral thesis within 30 days from the day of the defense in the national repository or the repository of the higher education institution." It is anticipated that this new legislation will enable

public access to all the future doctoral theses defended in Croatia (20).

Of note, publishing full theses is just the first step towards transparency. The importance of sharing data collected within the theses is also important, as well as meta-data. There is still a long way to go before accepting open data sharing in biomedical research (21, 22). One way to solve it at the level of a doctoral thesis is to require open data sharing concurrent with the thesis, whenever feasible. Furthermore, an important issue is the format in which theses were openly published. For example, PDFs could be searchable or not. Thus, it would be important to ensure the availability of searchable digital formats of doctoral theses.

We would like to emphasize that we spent months trying to obtain data on the defended theses. We experienced similar difficulties earlier when we wanted to study the success rates of PhD programs in medical schools in Croatia. However, the other schools did not want to share those data. Thus, we eventually focused only on the results of the University of Split School of Medicine (6). To our best knowledge, few PhD programs in Croatia have shown a willingness to be transparent about their results (7).

When looking into the published data of the Croatian Bureau of Statistics available on their website, which publishes the number of enrolled students per individual school and the number of defended PhD theses per university, the approximate calculation is that 20% of enrolled PhD students in Croatia have graduated (23, 24). Considering this low success rate, it is possible that Croatian educational institutions are not transparent about their defended PhD theses precisely because they do not want to advertise their subpar results in this segment. Institutions such as the Agency for Science and Higher Education (ASHE), which accredits educational programs in Croatian higher education institutions, could impose rules requiring transparency of success rates and details about the defended theses on publicly available institutional websites.

Limitations of the Study

A limitation of our study is reliance on multiple heterogeneous sources of information that could be possibly incomplete. Thus, we may have missed some PhD theses in our final counts. Furthermore, a limitation of the study could be the subjectivity of the access effort; namely, accessing one or a few doctoral theses on a topic would probably be much less effort than obtaining the entire catalogue or a full-text collection. Also, we aimed to cover the large observation period, which began in the 1990s when digitisation was in its infancy.

Conclusion

Accessing the list and full texts of defended PhD theses in medical schools in Croatia was an extremely challenging and laborious task. More transparency is needed about the defended PhD theses. It is of paramount importance to publish all PhD theses in open access in easily accessible repositories. This is important to align research policies with the demands for excellence that are expected from PhD programs and for understanding systematic errors in this field.

What Is Already Known on This Topic:
PhD theses should contain an original contribution to scholarship. Thus, they are essential part of new knowledge. Also, they can be the subject of various scientific analyses. Various studies have assessed, for example, the PhD thesis' quality of writing, bibliometric profile, research methodology, publication output, article/journal impact of the manuscripts published from the theses, and theses submission rules, among other topics. Accessibility of PhD theses is, thus, extremely important for enabling transparency and scrutiny.

What This Study Adds:
This study describes difficulties encountered when trying to access a list and full text of PhD theses defended in medical schools in Croatia. After contacting multiple sources of information, ranging from the National Bureau of Statistics, the National Library, and individual universities, institutions, and their websites, we could not find a single list of PhD theses. Obtaining a list of PhD theses required a month-long investigation. A central national list of PhD theses defended at state universities and freely available full-text theses would enable insight and transparency of defended PhD theses.

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Approval of the protocol by the Ethics Committee: The study protocol was approved by the Ethics Committee of the University of Split School of Medicine. The study was conducted in line with all the applicable ethical codes and laws.

Availability of Data and Materials: All raw data collected within the study are available on Open Science Framework (link: https://osf.io/hz52g/).

Conflict of Interest: The authors declare that they have no conflict of interest.

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The Use of Pressure Recording Analytical Method in Patients Undergoing Endovascular Repair for Abdominal Aortic Aneurysm: The Impact on Clinical Decisions for the Appropriate Postoperative Setting and Cost-effective Analysis

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Abstract

Objective. To analyze the use of the Pressure Recording Analytical Method (PRAM), an hemodynamic monitoring system, in evaluating intraoperative and postoperative hemodynamic instability in patients undergoing endovascular repair for abdominal aortic aneurysm, and to evaluate if the decision to refer patients to a ordinary ward or to a Cardiac Step-Down Unit (CSDU) after the intervention on the basis of intraoperative hemodynamic monitoring could be more cost-effective. **Materials and Methods.** After preoperative clinical evaluation, 44 patients were divided in this non-randomised study into two groups according to their postoperative destination: Group 1-ward (N=22) and Group 2-CSDU (N=22). All patients underwent monitoring with PRAM during the intervention and in the 24 postoperative hours, measuring several indices of myocardial contractility and other hemodynamic variables. **Results.** According to the variability of two parameters, Stroke Volume Variation and Pulse Pressure Variation, patients were classified as stable or unstable. Unstable patients showed a significant alteration in several hemodynamic indices, in comparison to stable ones. According to the intraoperative monitoring, eight high risk patients could have been sent to an ordinary ward due to their stability, with a reduction in the improper use of CSDU and, consequently, in costs. **Conclusions.** Hemodynamic monitoring with PRAM can be useful in these patients, both for intraoperative management and for the choice of the more appropriate postoperative setting, possibly reducing the improper use of CSDU for hemodynamically stable patients who are judged to be at high risk preoperatively, and re-evaluating low surgical risk patients with an unstable intraoperative pattern, with a possible reduction in costs.

Key Words: Hemodynamic Monitoring ▪ Goal Directed Therapy ▪ Abdominal Aortic Aneurysm ▪ Endovascular Repair ▪ Postoperative Setting

Introduction

Hemodynamic monitoring is crucial in critically ill patients (1-3) as well as during and after major surgery (1, 4, 5-7), in order to promptly detect the occurrence of acute alterations, such as shock, that could lead to hypoperfusion and organ ischemia, and to evaluate the effects of pharmacological interventions.

In patients who are candidates for major vascular surgery, postoperative complications and death are more frequent among high risk and older patients, since they have multiple comorbidities, such as coronary artery disease, heart failure, diabetes mellitus and chronic renal dysfunction (8). In order to reduce cardiac perioperative complications in these patients, several authors have underlined the importance of a complete preoperative

cardiac evaluation (9) and therapy optimization (10, 11), whereas the role of preoperative coronary revascularization is still debated (9, 12). In the last few years, therapy optimization, known as Goal-Directed Therapy (GDT), guided by data collected during hemodynamic monitoring, has been associated with a reduction in the incidence of surgical complications and length of hospital stay, even if the data regarding periprocedural mortality after major visceral/non-cardiac surgery are still controversial (6, 7, 13, 14). Nevertheless, even the NICE (National Institute for Health and Care Excellence) Guidelines recommend GDT for patients undergoing major vascular surgery (15).

The GDT cornerstone consists mainly in the monitoring of cardiac output in order to optimize perfusion and tissue oxygenation, and to improve postoperative outcomes, by guaranteeing adequate oxygen delivery (16, 17). This suggests that a safe hemodynamic monitoring system is required, and with this aim, several systems have been developed which can analyze variations in cardiovascular and hemodynamic parameters, and provide information on cardiac and vascular interaction (18).

Among them, the Pressure Recording Analytical Method (PRAM) system has been widely used in our Institution to evaluate hemodynamic parameters in several cardiac conditions, such as heart failure and acute myocardial infarction (19-21). PRAM is a minimally invasive monitoring system that provides, from the beat-to-beat analysis of the arterial waveform, measurement of the main hemodynamic variables, such as systemic blood pressures, stroke volume, cardiac output, and vascular resistances. Moreover, dynamic indices of fluid responsiveness are continuously displayed (17).

The aim of this prospective, single center study was to evaluate the impact of the use of this minimally invasive hemodynamic monitoring system on the prediction of postoperative hemodynamic instability after endovascular repair of an abdominal aortic aneurysm (AAA). Moreover, we compared the decision to refer patients to the postoperative ward or the Cardiac Step-Down Unit (CSDU) on the basis of preoperative assessment or intraoperative monitoring, to evaluate whether this latter decision could lead to a reduction in the improper use of CSDU. Finally, we performed a cost analysis of these two different strategies.

Materials and Methods

From December 2019 to April 2020, all patients who were candidates to endovascular repair for AAA at our Department were prospectively enrolled and gave their informed consent for participation in the study. The inclusion criteria were: age over 18 years, the presence of an AAA with an indication for endovascular repair, and the possibility of radial arterial access. The exclusion criteria were: difficulty in obtaining an adequate arterial signal in the radial artery (for example, due to a disease affecting the subclavian artery), and the need for more complex procedures, such as fenestrated, branched or Chimney EVAR (FEVAR, BEVAR and ChEVAR, respectively). As previously reported in the study by Abebe et al., the incidence of hemodynamic instability in adult surgical patients in the post-anesthesia care unit ranges from 21.1% to 56.6% and is about three times higher in patients with high versus low risk (22). Hypothesizing an anticipated incidence of hemodynamic instability of 20% in low risk patients and a 60% incidence in high risk patients, considering a type I error of 0.05 and a type II error of 80%, the number of patients needed is 44, 22 in each group. The study protocol was drawn up in accordance with the ethical Guidelines of the 1964 Declaration of Helsinki and was an extension of a larger study concerning the use of PRAM in patients undergoing transcatheter aortic interventions, previously approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria Careggi (reference number Cineca 11574).

Preoperative Assessment and Indications for Surgery

According to the Guidelines (23), the indication for elective surgery was the presence of asymptomatic infrarenal AAA ≥5.5 cm in male patients, whereas in females the threshold diameter for elective surgery was > 5 cm. Intervention was also

considered if the diameter was under the threshold but one or more of the following conditions were present: rapid aneurysm growth (>1 cm annually or >0.5 cm within 6 months), and AAA morphology considered as high risk of rupture (i.e. saccular aneurysm or in the presence of blisters, blebs or inhomogeneous parietal thrombus).

All patients underwent computed tomography angiography of the entire thoraco-abdominal aorta. Preoperative evaluation assessing the feasibility of an endovascular procedure was performed using Aquarius iNtuition® software (TeraRecon, Foster City, California, USA). All patients underwent complete laboratory tests (blood count, creatinine, transaminases and coagulation) and a complete cardiovascular evaluation, including electrocardiography, echocardiography, stress test or coronary angiography when indicated, duplex ultrasonography of the supra-aortic trunks and lower extremities, and pulmonary function testing. A preoperative anesthesiology evaluation was performed to determine the need for perioperative and postoperative intensive monitoring. High risk patients were defined according to the EVAR-2 trial: recent acute myocardial infarction (<3 months), symptomatic congestive heart failure, unstable angina, severe valvular heart disease, cardiac arrhythmia, chronic obstructive pulmonary disease, and chronic kidney disease with a serum creatinine value of >2.26 mg/dL (24).

On the basis of the preoperative assessment, the patients were prospectively divided into two groups and in all cases the anesthesiologist followed the preoperative indications for postoperative monitoring: Group 1-ward (N=22), patients for whom postoperative CSDU was not required, and Group 2-CSDU (N=22), patients for whom postoperative CSDU was required. No random allocation into the two groups was performed. All patients underwent intraoperative monitoring with the minimally invasive PRAM system (25) using a MostCareUp® device (Vygon, Ecouen, France), both during the intervention and for the first 24 postoperative hours, both on the ward and in the CSDU.

Furthermore, the patients were divided on the basis of hemodynamic parameters detected intraoperatively into an "unstable" group and a "stable" group. The "unstable" group consisted of 18 patients in whom the variability of stroke volume variation (SVV) and pulse pressure variation (PPV) measured during the intervention and in the first subsequent 24 hours was greater than 15%, while the "stable" group consisted of 26 patients in whom the fluctuations in these parameters were less than 15% and were considered physiological, as previously reported in the literature (26-29).

PRAM System

The MostCareUp® monitoring system is a device that makes it possible to perform a beat-to-beat analysis, from which it is possible to obtain several hemodynamic variables and the parameters of myocardial contractility (heart-circulation interactions, variations in ventricular contractility, arterial stiffness, etc.) (Supplemental Figure 1). This medical device is CE marked (identification number CE 0476). This system does not require calibration, and does not use pre-estimated values obtained from statistical analyses or anthropometric data (i.e. gender or age) that belong to the patient monitored. For PRAM set-up, height and weight data are required in order to obtain body surface area which is necessary to obtain the parameters indexed in relation to the patient's size, such as cardiac index and stroke volume index. Therefore, the hemodynamic parameters detected by this system are influenced exclusively by the morphology of the pressure signal recorded in the patient analyzed. Consequently, when the clinical condition of the patient modifies the dynamic impedance of the cardiovascular system (changes in vascular tone due to the effect of vaso-active drugs, as well as variations in venous return, hematocrits, the rigidity of the vessels and heart circulation coupling, etc.), the system obtains the new information from the variation in the morphology of the pressure wave detected at the peripheral level. The PRAM method therefore provides a large amount of information about the patient's hemodynamic status, while keeping the level of invasiveness contained, thus being easily applicable

to almost all patients, in particular in the field of vascular surgery.

For PRAM monitoring, a standard arterial catheter was inserted into the radial artery. A 150 cm pressure tube connection and transducer (Truwave PX-600F, Edwards Lifecsience, Irvine, CA, USA) were connected to the MostCareUp® monitoring system (Vygon, Ecouen, France). Pressure signals were sampled at 1000 Hz. An event marker of the signal pressure recordings was used to identify the phases of the study. The variables obtained by PRAM were displayed on the screen in real time and stored electronically (every 30 seconds) in the system.

During monitoring the following variables were evaluated: systolic, diastolic, dicrotic and mean arterial pressure (mmHg); Heart Rate (HR, bpm); Stroke Volume (SV, mL); Stroke Volume Index (SVI); Cardiac Output (CO = SV x HR, L/min); Cardiac Index (CI); Systemic Vascular Resistances (SVR, dyne*s/cm); Stroke Volume Variation (SVV); Pulse Pressure Variation (PPV); and Cardiac Cycle Efficiency (CCE, units) that indicates the ability of the cardiovascular system to maintain homeostasis at different energy levels.

The reliability of the PRAM measurements has been previously analyzed and demonstrated (30). Given the results of that study in our Institution we use, in the presence of resonance artifacts, a dedicated transducer, manufactured for limiting resonance effects. Also, the validity of the hemodynamic parameters measured by PRAM has been previously analyzed and demonstrated in comparison with echocardiographic assessment of CO (31), non-invasive measurements of blood pressure values (32), thermodilution for assessment of CI (1), and with both thermodilution and another more invasive monitoring system for CO assessment (33).

Use of PRAM in Different Clinical Settings

In the last 20 years, the PRAM system has been used in different clinical conditions, both in our Center and in other Centers. In particular, in our Center it has been used to monitor patients with decompensated heart failure treated with ultrafiltration and diuretics (19, 20), as well as to evaluate the beneficial effects of levosimendan (34), in patients with atrial fibrillation undergoing electrical cardioversion (35), in patients with ST-Elevation myocardial infarction treated with primary angioplasty (21), to monitor patients undergoing transcatheter aortic valve replacement (36, 37), and in patients undergoing cardiac and vascular surgery, both intraoperatively (32) and in the postoperative course of cardiac surgery (4). In other Centers, the PRAM system has been used to monitor patients with septic shock (38), in patients undergoing major abdominal surgery (39) or cardiac surgery (1, 40). Moreover, PRAM has been also used in pediatric patients (41-43), in patients under spinal anesthesia for elective cesarean section (44), and in patients with veno-venous extracorporeal membrane oxygenation therapy (45).

Statistical Analysis

All data were recorded prospectively in a dedicated database, containing clinical and anatomic characteristics, intraoperative and postoperative variables detected with MostCareUp®, blood tests, length of stay and 30-day MACCE (Major Adverse Cardiac and Cardiovascular Events). The results were expressed as the means and standard deviation of the hemodynamic parameters in the intraoperative and 24-hour postoperative periods. Differences in percentages were analyzed by means of the Chi-square test or Fisher exact test for frequencies smaller that 5%, while differences in mean values were compared by means of the T-test for unpaired data. The mean values of the hemodynamic parameters measured in these two groups were then compared by means of the T-test for unpaired data. Finally, a cost analysis was performed in order to assess the potential savings associated with correcting the overuse of unnecessary postoperative CSDU stays. For this cost analysis we considered that in our Institution hospitalization in a surgical ward costs 766 euros per day, while it costs 1188 euros per day in the CSDU. Moreover, we estimated a cost of about 120 euros per patient for 72 hours hemodynamic monitoring with PRAM.

Results

Demographic and Clinical Features

The patients were predominantly male in both groups, with no significant difference in mean age or in the prevalence of cardiovascular risk factors and comorbidities. These were well balanced in the two groups, also with regard to the prevalence of coronary artery disease and peripheral occlusive arterial disease (Table 1). Regarding anatomical and technical features, the diameters of the aneurysm and the iliac arteries were similar in the two groups, and in about 1/3 of the cases a percutaneous approach was possible in both groups (Table 1), while in the remaining patients a surgical approach was required.

No statistically significant differences were found between the group 1-ward and group 2-CSDU patients in the hemodynamic variables assessed both intraoperatively and in the subsequent 24-hour monitoring (Table 2).

Table 1. Clinical, Anatomical and Procedural Characteristics of Patients Investigated

Characteristics	Group 1-ward	Group 2-CSDU	P
Clinical			
Age (mean ± SD)	74±6	77±6	0.105
Sex (M) (N; %)	21 (95.5)	20 (90.9)	0.550
Arterial Hypertension (N; %)	17 (77.3)	15 (68.2)	0.498
Diabetes Mellitus (N; %)	1 (4.5)	4 (18.2)	0.345
Hyperlipidemia (N; %)	12 (54.5)	12 (54.5)	1
COPD (N; %)	14 (63.6)	16 (72.7)	0.517
CAD (N; %)	4 (18.2)	9 (40.9)	0.099
POAD (N; %)	1 (4.5)	5 (22.7)	0.185
Anatomical and technical features			
AAA mm (mean ±SD)	52.9±7.3	56.2±8.5	0.174
R-CIA mm (mean ±SD)	19.4±6.2	17.5±4.4	0.248
L-CIA mm (mean ±SD)	17.7±6.7	18.7±5.8	0.599
Percutaneous access (N;%)	8/22 (36.4)	6/22 (27.3)	0.517

COPD=Chronic Obstructive Pulmonary Disease; CAD=Coronary Artery Disease; POAD=Peripheral Occlusive Arterial Disease; AAA=Abdominal Aortic Aneurysm; CIA=Common Iliac Artery; R=right; L=left.

Table 2. Intraoperative and 24 Hours Postoperative Hemodynamic Variables in the Two Groups, of Patients Analyzed, Ward (group 1) and CSDU (group 2).

Hemodynamic variables	Intraoperative			24 hours postoperative		
	Group 1 -ward	Group 2 -CSDU	P*	Group 1-ward	Group 2 -CSDU	P*
Systolic pressure (mmHg)	119.5±17.5	125.0±22.8	0.375	135.9±17.4	138.4±15.8	0.620
Diastolic pressure (mmHg)	61.4±6.7	62.3±11.2	0.748	61.9±10.3	65.1±7.9	0.254
Heart rate (bpm)	60.9±7.5	65.6±9.0	0.067	71.9±17.4	71.8±19.0	0.986
Systemic vascular resistances (dyne·s/cm^5)	1233.9±196.2	1327.9±227.9	0.150	1388.3±250.3	1436.5±209.7	0.493
CCE (units)	0.036±0.02	0.005±0.30	0.631	0.080±0.30	-0.010±0.30	0.325
Cardiac Output (L/min)	4.6±0.6	4.6±0.6	1	4.6±0.6	4.6±0.7	1
Stroke volume (mL)	74.9±13.1	77.2±11.1	0.533	68.0±13.1	71.0±23.1	0.599
SVV (%)	12.6±5.8	11.8±4.9	0.624	13.6±6.3	13.7±3.7	0.949
PPV (%)	17.9±1.6	15.3±7.6	0.124	19.4±13.7	16.8±8.7	0.457

*T test for unpaired data was used to compares the means of the two groups; CSDU=Cardiac Step Down Unit; CCE=Cardiac Cycle Efficiency; SVV=Stroke Volume Variation; PPV=Pulse Pressure Variation.

Hemodynamic Variables ("Unstable" vs. "Stable" group)

Comparing the two groups of unstable vs. stable patients, no significant differences were observed in mean systolic and diastolic pressure values, while heart rate, SVR, CCE, CO and SV differed significantly between these two groups, both in the intraoperative and in the 24-hour postoperative phase (Table 3). Interestingly, the average CCE in the "unstable" group was negative both during surgery and in the 24-hour postoperative monitoring.

Considering this division, 18 patients belonging to group 1-ward were considered "stable" and four "unstable" according to our criteria, while in group 2-CSDU, eight patients were deemed to be "stable" and 14 "unstable" (Figure 1).

A significant difference was observed in unstable patients between group 1–ward and group 2–CSDU patients (18.2% vs. 63.6%, P=0.002). In 5/44 unstable patients (11.4%), vasopressors were required for persistent hypotension.

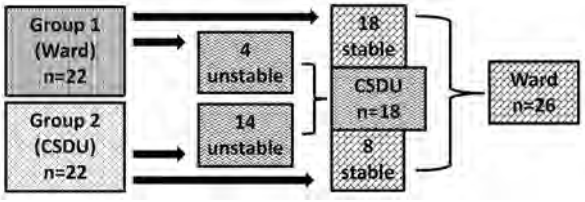

Figure 1. Real and hypothetical subdivision of patients destination, ward or CSDU, on the basis of preoperative assessment and after hemodynamic variables monitoring.

From this study it emerges that there were 4/22 (18.2%) patients referred to the non-monitored ordinary ward who could have benefited from postoperative monitoring. On the other hand, eight patients (36.4%) who were referred to the CSDU were very stable and could have been sent to the ward according to the intraoperative hemodynamic monitoring evaluation. In fact, taking into account a hypothetical subdivision carried out with the contribution of intraoperative hemodynamic variables, we would have sent 26 (18+8) patients to the ordinary ward, and 18 (4+14) patients to CSDU (Figure 1).

In Figure 2 we present the trends of the CCE-curves obtained intraoperatively and in the postoperative 24 hours in two paradigmatic patients: on the left a "stable" patient sent to CSDU and on the right an "unstable" patient sent to the ward, on the basis of preoperative evaluation.

The patient on the left, sent to the CSDU after preoperative evaluation, shows a regular trend in both intraoperative and postoperative parameters, a sign that his cardiovascular system was able to compensate for the perturbations induced by anesthesia and surgery. On the other hand, the patient on the right, sent to the non-monitored ward, shows significant variability in both intraoperative and postoperative hemodynamic parameters, which means the reduced compliance of his cardiovascular system, a condition with a higher risk of complications (Supplemental Figures 2 and 3).

During 30-day follow-up we did not observe any perioperative deaths, and none of the 44

Table 3. Intraoperative and 24 Hours Postoperative Hemodynamic Variables in the Two Groups, of Stable and Unstable Patients

Hemodynamic variables	Intraoperative			24 hours postoperative		
	Unstable	Stable	P*	Unstable	Stable	P*
Systolic pressure (mmHg)	121.3±21.1	122.8±8.9	0.760	133.5±19.8	139.7±17.5	0.277
Diastolic pressure (mmHg)	64.9±10.9	59.6±8.5	0.079	66.9±11.1	65.1±7.9	0.539
Heart rate (bpm)	67.9±7.2	59.2±8.9	0.0009	78.6±19.1	65.9±13.4	0.014
Systemic vascular resistances (dyne·s/cm^5)	1418.6±236.7	1178.8±192.2	0.0006	1544.3±235.2	1314.2±113.1	0.0002
CCE (units)	-0.212±0.2	0.184±0.2	0.0001	-0.201±0.2	0.210±0.1	0.0001
Cardiac Output (L/min)	4.3±0.5	4.8±0.6	0.0045	4.3±0.5	4.9±0.6	0.0008
Stroke volume (mL)	70.2±9.8	77.9±14.1	0.042	59.0±17.1	77.1±16.9	0.001

*T test for unpaired data was used to compares the means of the two groups; Unstable patients were defined as those who showed values of SVV and PPV higher than 15%. CCE=Cardiac Cycle Efficiency.

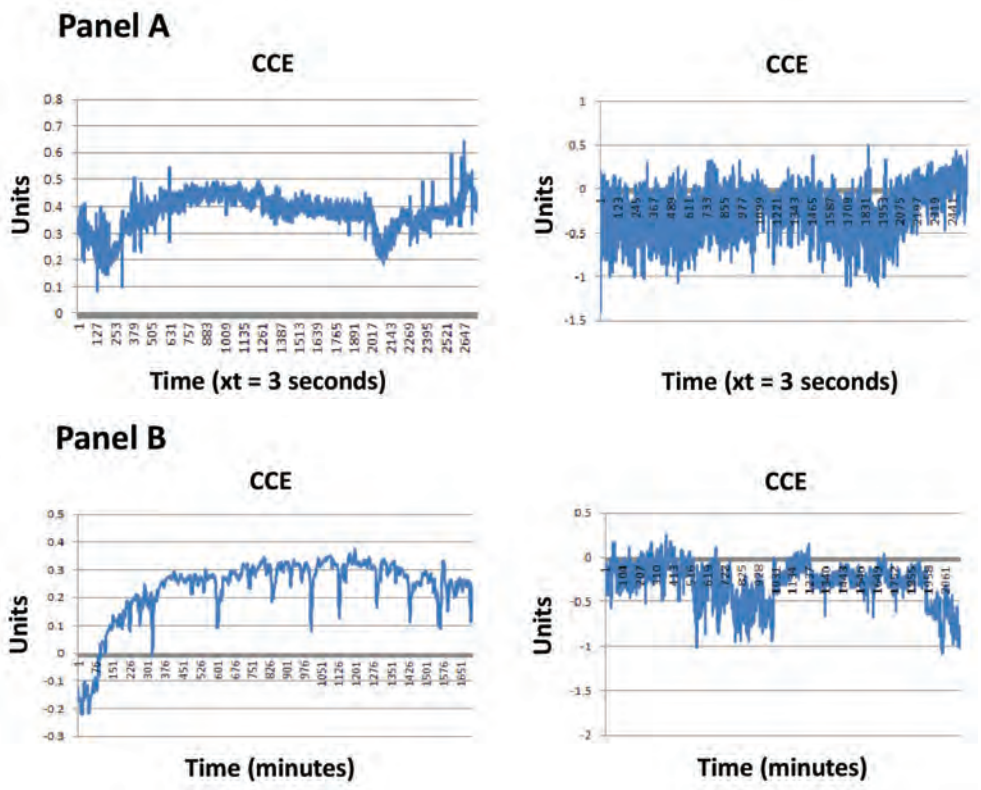

Figure 2. Trends of the CCE curves in the intraoperative phase (panel A) and in the 24 postoperative hours (panel B) of two paradigmatic patients: on the left a «stable» patient sent to the CSDU and on the right an «unstable» patient sent to the ward on the basis of preoperative evaluation.

patients had postoperative cardiac complications. The mean length of hospital stay was 4.28 days in group 1 and 5.26 days in group 2.

Cost Analysis

Considering the different costs of hospital stay per day at our Institution in a ordinary surgical ward (766 euros) and in the CSDU (1188 euros), we can calculate that the improper referral of a patient to the CSDU costs 422 euros per day more than if he was sent to the ward. According to our study, eight patients were improperly referred to the CSDU, with an estimated increase in costs of 3376 euros. Considering that 44 patients undergoing endovascular treatment are admitted over five months, we can assume that we treat 106 AAA patients in one year at our Institution, of whom about 20 are improperly referred to the CSDU after preoperative assessment, with an additional cost of 8440 euros per year in this selected group of patients. It is likely that this strategy could also be applied to other diseases in order to improve cost savings. The counterpart of our study is, however, represented by the group of patients sent to the ward according to preoperative evaluation but who would have benefited from CSDU according to hemodynamic monitoring. Assuming a cost of about 120 euros per each patient for PRAM monitoring, we can estimate an annual expense of approximately 2400 euros for 20 patients that must be deducted from the total profit.

Discussion

In the present study we report the feasibility and effectiveness of hemodynamic monitoring in patients undergoing endovascular repair for AAA, in order to choose the appropriate postoperative setting and its possible impact on costs. To date, this

choice at our Institution has been mainly based upon clinical and instrumental preoperative evaluation, guided by our previous studies (46, 47) in accordance with the current Guidelines (23).

In fact, in one of our previous studies, the importance of a complete preoperative cardiac evaluation in patients undergoing abdominal aortic surgery was underlined and, in particular, we demonstrated that patients with a positive ergometric test could benefit from endovascular treatment to reduce the cardiac complications associated with open surgery (46). Moreover, in another study (47) we compared two different strategies of preoperative cardiac evaluation: one considering each patient's cardiovascular risk, and another applying the Lee criteria (48). This study did not demonstrate any significant difference between the two strategies in either morbidity or mortality, and suggested that routine use of ergometric testing should be avoided, since in most cases coronary angiography and myocardial revascularization do not lead to any significant improvement in morbidity and mortality. These studies were in line with the recent recommendations of the European Society of Vascular Surgery, suggesting that further cardiac assessment should be reserved only for patients with an acute cardiovascular disease, such as unstable angina, decompensated heart failure, severe valvular disease, and significant arrhythmias. In the absence of these diseases, clinical cardiovascular risk factors and the patient's functional capacity should be evaluated, and invasive coronary angiography should follow the same indications as in a non-surgical setting and not be routinely used for perioperative risk assessment before aortic surgery (23).

As far as intraoperative and postoperative management is concerned, fluid therapy and vasoactive drugs during interventions have been shown to play a pivotal role in these patients' outcomes (49). In order to improve intraoperative management, in the last few years the concept of Goal-Directed Therapy has progressively emerged (5, 13, 14, 16), and is also applied to vascular surgical patients (50, 51). For this purpose, hemodynamic monitoring is necessary, for which several devices have been developed (17, 18). Among them are the "Pulse Contour Methods" (PCMs) systems which are based on the principle that the volume of blood ejected from the left ventricle in systole (Stroke Volume, SV) could be estimated by dividing the area subtended by the pressure curve by the dynamic impedance of the arterial system. PCMs system can be classified into three categories: PCMs that require extreme calibration, through the dilution of an indicator; PCMs using the anthropometric and demographic data of the patient under study, and PCMs that do not require calibration or pre-estimated data. The MostCareUp® belongs to the third group of PCMs and uses the PRAM (Pressure Recording Analytical Method) system, based on the physical principle of perturbation, according to which every physical system subjected to perturbation tends to react by seeking a new condition of stability (i.e. a condition of minimum energy required).

This device has been previously explored at our Institution in several acute cardiac conditions, such as heart failure (19, 20) and ST-segment Elevation Myocardial Infarction (21), as well as in the postoperative phase of cardiac surgery. In the latter study, reduced perioperative values of Cardiac Cycle Efficiency demonstrated a negative prognostic impact at six months follow-up (4).

In the present study, we used this device to monitor two groups of patients undergoing endovascular repair for AAA: group 1 consisted of patients at low risk from preoperative assessment, who were referred to an ordinary ward after the intervention, and group 2 were those for whom postoperative CSDU monitoring was planned.

Comparing the results obtained from group 1 and 2 patients, no statistically significant difference was found in any of the variables analyzed with PRAM (MostCare®-UP), either during intraoperative monitoring or in the 24 hours after the intervention. However, the standard deviations of the hemodynamic parameters measured were wide, indicating the high variability of data collected, and suggesting that hemodynamic parameters varied greatly from patient to patient during surgery, independently of the destination assigned on the basis of the preoperative evaluation.

On the basis of these results, we systematically re-evaluated the trends of all the parameters analyzed in each patient, and observed that patients who showed a stable trend in hemodynamic variables during surgery remained stable even in the 24 postoperative hours, and were classified as "stable". On the other hand, patients who showed a higher degree of hemodynamic parameter variability during surgery maintained that variability in the postoperative period, and were defined as "unstable".

Therefore, according to their hemodynamic measurements, we divided patients into stable and unstable groups, a classification that did not exactly correspond to the group 1-ward and group 2-CSDU classification obtained according to risk stratification after preoperative evaluation. This may reflect the difficulties often found in cardiac risk stratification in patients who are candidates for vascular surgical interventions, suggesting the utility of a continuous and minimally invasive intraoperative monitoring system that could further help in guiding anesthetists in the choice of the more appropriate postoperative setting.

In particular, patients judged to be at low surgical risk following multidisciplinary preoperative evaluation, but who showed "latent" cardiovascular hemodynamic alterations, as highlighted by the reduced compliance of the cardiovascular system assessed with PRAM during surgery, could be referred to the CSDU in order to avoid perioperative complications and prevent their occurrence. On the other hand, this study also demonstrated that there are patients deemed to be at intermediate or high surgical risk after preoperative clinical and instrumental evaluation that show markedly stable hemodynamic parameters during intraoperative monitoring, and that could be referred to an ordinary ward instead of the CSDU.

This could also have an impact on costs: in fact, according to our cost analysis, in the present study we estimated a cost saving of approximately 6000 euros per year by avoiding the improper use of the CSDU, thus leading to the creation of a model that could also be applied to other clinical conditions in addition to AAA endovascular repair, with a further reduction in costs.

Our study does not seek to underestimate the importance of preoperative evaluation, as confirmed by the higher prevalence of unstable patients observed in group 2 (high risk) vs. group 1 patients (63.6 vs. 18.2%, P=0.002). Interestingly, our study also provides data about hemodynamic instability in a group of patients treated with an elective endovascular repair procedure, for whom hemodynamic monitoring data are scarce, since they were mainly analyzed in the context of a ruptured AAA, as demonstrated in a previous meta-analysis (52).

Conclusion

In patients with AAA who are undergoing endovascular repair, intraoperative hemodynamic assessment with PRAM could represent a helpful strategy for surgical risk stratification and, in particular, could be useful for choosing the better clinical postoperative setting for each patient, together with the preoperative clinical and instrumental evaluation. The consequent reduction in the improper use of the CSDU could also have a beneficial impact on costs.

What Is Already Known on This Topic:

Hemodynamic monitoring is crucial in critically ill patients, both during and after major surgery, in order to promptly detect the occurrence of acute alterations that could lead to hypoperfusion and organ ischemia, and to evaluate the effects of pharmacological interventions. In patients who are candidates for major vascular surgery, postoperative complications and death are more frequent among high risk and older patients, since they have multiple comorbidities. A complete preoperative cardiac evaluation and therapy optimization have a crucial role in reducing cardiac perioperative complications. In the last few years, therapy optimization guided by hemodynamic monitoring, the Goal-Directed Therapy (GDT), has been associated with a reduction in surgical complications and the length of hospital stay. The GDT consists mainly in cardiac output monitoring to optimize perfusion and tissue oxygenation, and to improve postoperative outcomes. With this aim, several hemodynamic monitoring systems have been developed, such as the Pressure Recording Analytical Method (PRAM) system.

What This Study Adds:

Hemodynamic monitoring with PRAM in patients undergoing endovascular repair for abdominal aortic aneurysm can be useful, both for intraoperative therapeutic management and for the choice of the more appropriate postoperative setting for each patient, which is usually decided on the basis of preoperative clinical and instrumental evaluation.

This strategy could lead to avoiding the improper use of the Cardiac Step-Down Unit (CSDU) in stable patients judged to be at high surgical risk preoperatively, and to re-evaluate low surgical risk patients who show an unstable pattern during intraoperative monitoring. The reduction in the improper use of the CSDU could also have a beneficial impact on costs.

Authors' Contributions: Conception and design: EG, SMR and CP; Acquisition, analysis and interpretation of data: WD, CG, NM and AC; Drafting the article: EG, SMR, CP and EC; Revising it critically for important intellectual content: WD, CG and TAF; Approved final version of the manuscript: NM, RP and EC.

Conflict of Interest: Dr. Salvatore Mario Romano is the owner of the patent of the Pressure Recording Analytical Method.

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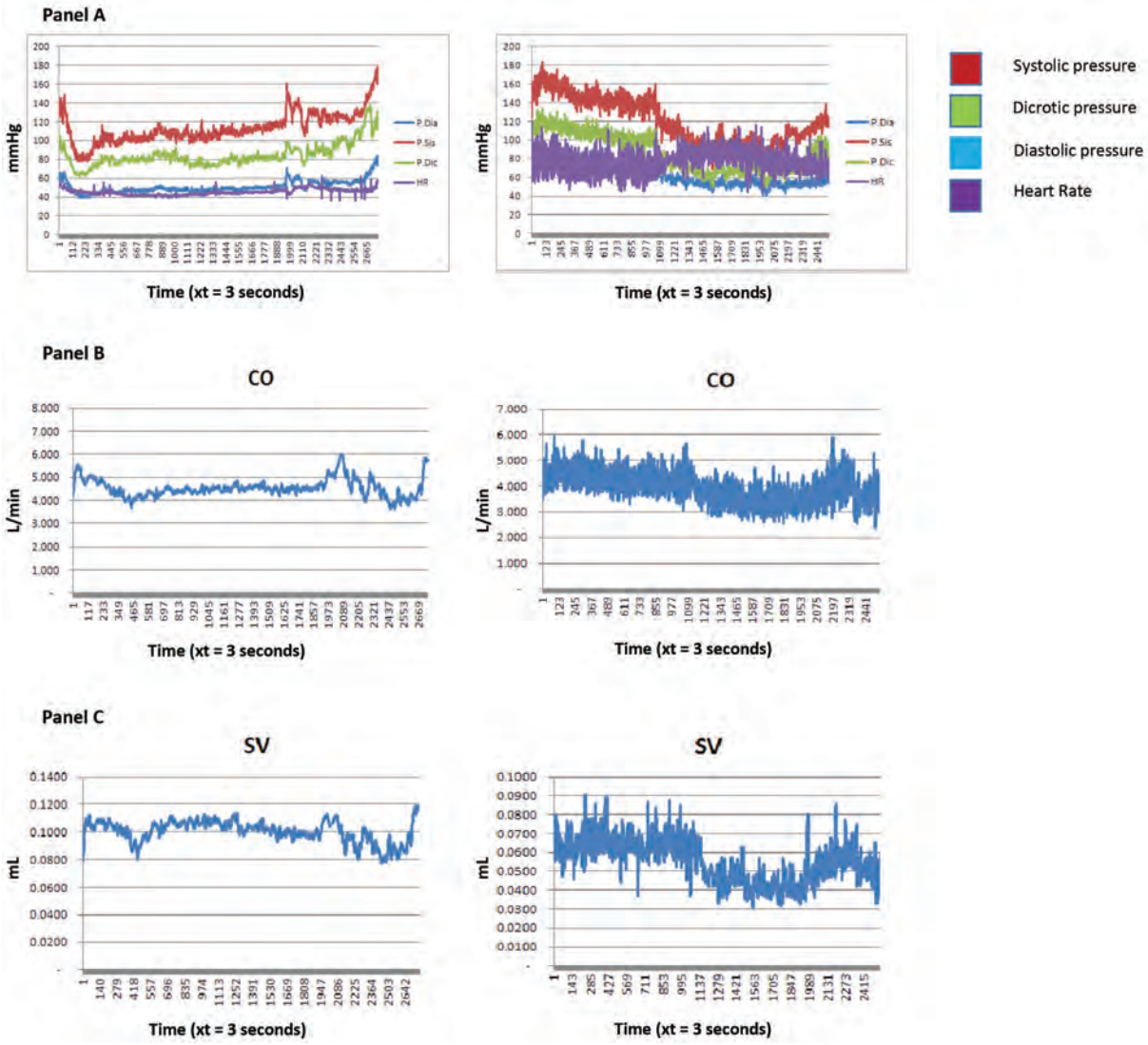
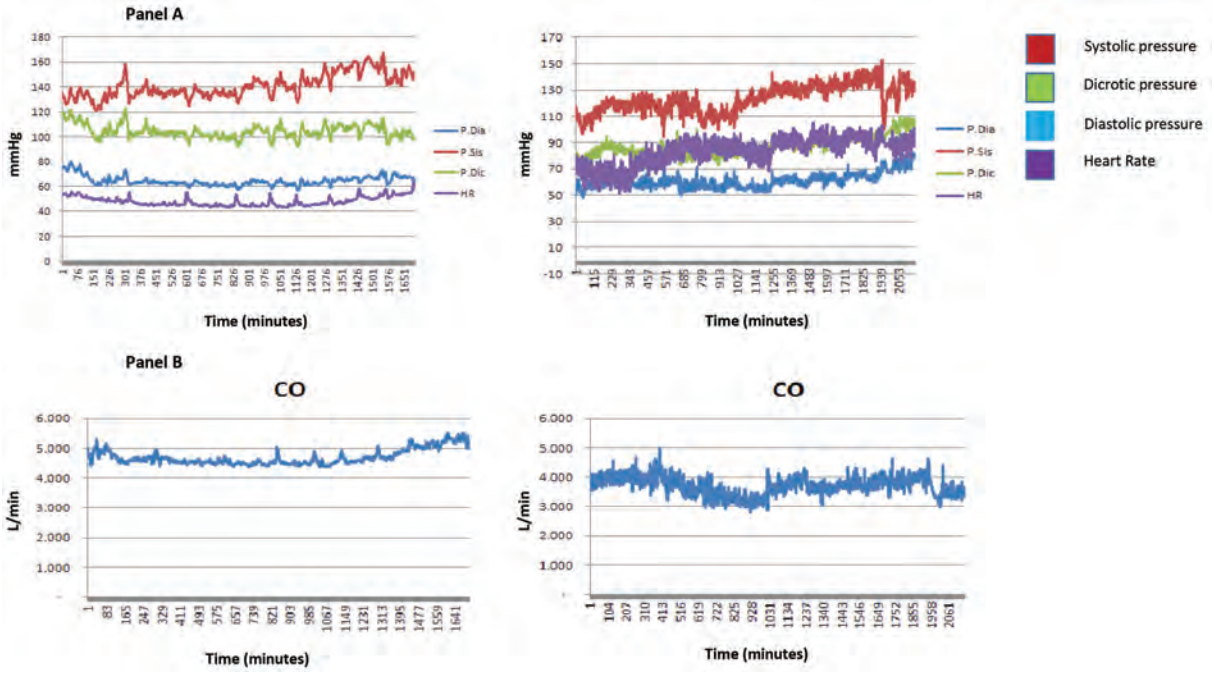
Supplementary Figures

Supplemental Figure 1. Image of MostCareUp® showing the main hemodynamic variables and indices of myocardial contractility assessed with PRAM algorithm.



Supplemental Figure 2. Trends of hemodynamic variables (systolic, dicrotic and diastolic pressure and heart rate) (panel A), of CO (panel B) and of SV (panel C) in the intraoperative phase of two paradigmatic patients: on the left a «stable» patient sent to the CSDU and on the right an «unstable» patient sent to the ward on the basis of preoperative evaluation.



Supplemental Figure 3. Trends of hemodynamic variables (systolic, dicrotic and diastolic pressure and heart rate) (panel A) and of CO (panel B) in the 24 postoperative hours of two paradigmatic patients: on the left a «stable» patient sent to the CSDU and on the right an «unstable» patient sent to the ward on the basis of preoperative evaluation.

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Autonomic Dysfunction in Amyotrophic Lateral Sclerosis – A Case-Control Study

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Abstract

Introduction. This study aimed to explore autonomic nervous system involvement in amyotrophic lateral sclerosis (ALS) patients by evaluating sympathetic skin response (SSR). **Materials and Methods.** The study included 35 sporadic (ALS) patients (cases), and 35 healthy age and sex-matched participants (controls) aged <60 years. SSR was recorded in the electrophysiology lab of the Neurology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Patients with diseases associated with peripheral or autonomic neuropathy were excluded. Prolonged latency (delayed SSR) or an absent response was considered abnormal SSR. **Results.** SSR was found to be abnormal in 17 (48.6 %) ALS cases, with an absent response in the upper limbs of six cases (17.1%). Abnormal SSR was more prevalent in the lower limbs, with 33 (94.3%) and 20 (57.1%) cases having a delayed or absent response, respectively. In comparison, SSR was normal in all control participants (P-value <0.05). Abnormal SSR was significantly more common in the lower limbs of ALS cases with bulbar palsy than those without bulbar palsy (P-value=0.04). There was no association of SSR with disease severity and duration. **Conclusion.** ALS is significantly associated with abnormal SSR, indicating autonomic nervous system involvement. There could also be an association between bulbar palsy and abnormal SSR among ALS patients. Further studies should be carried out to determine the association of abnormal SSR with disease severity, duration, and type.

Key Words: Amyotrophic Lateral Sclerosis ▪ Sympathetic Skin Response ▪ Autonomic Nervous System ▪ Motor Neuron Disease.

Introduction

Motor neuron disease (MND) is a group of neurodegenerative diseases primarily affecting the motor nervous system (1). Amyotrophic lateral sclerosis (ALS) is the most common form of MNDs, which involves both upper and lower motor neurons (2). The incidence and prevalence of ALS differ from country to country. The incidence may range from as low as 0.26 per 100,000 person-years in Ecuador, to as high as 23.46 per 100,000 person-years in Japan. The point prevalence may vary from 1.57 per 100,000 in Iran to 11.80 per 100,000 in the United States (3). The mean and median age of ALS onset is between 51 and 66 years (4). However, 5-10 % of ALS could be inherited, and genetic mutation is responsible for nearly 60% of inherited cases (5). The putative mechanisms are the death of motor neurons owing to protein aggregation, glutamate excitotoxicity, mitochondrial dysfunction, impaired axonal transport, growth factor deficiency, inflammation, and apoptosis (6).

Once considered a pure motor disease, non-motor manifestations, including autonomic dysfunction, may also occur in ALS. Recent studies have suggested that subclinical impairment of

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cardiovascular, sudomotor, gastrointestinal, salivary, and lacrimal regulation may occur in ALS even in the early stages (7–9). Besides, ALS patients may die suddenly due to circulatory collapse (7). Among the numerous autonomic manifestations, sudomotor impairments can be assessed simply by clinical and investigation methods. Sympathetic skin response (SSR) is a test of sympathetic autonomic function that records the transient change of the electrical potential of the skin generated by activated sweat glands. The reflex arc of SSR is formed by the somatic sensory afferent limb, the central pathway, and the autonomic sympathetic efferent limb. This response is activated with different internal or externally applied arousal stimuli (10). SSR can be quickly recorded in an electrophysiology lab by most electromyography (EMG) equipment using the surface electrodes. The latency and amplitude of the SSR are recorded in both upper and lower limbs. SSR is a nonspecific test, and abnormalities can be found in autonomic or somatic neuropathy (10). However, this test can be helpful in ALS, which was previously mainly considered to be a disease involving only the motor nervous system, but some recent studies have reported cutaneous vasomotor and sudomotor dysfunction of varying severity in ALS patients (11, 12). In these studies, ALS patients were found to have abnormal latency, amplitude, or absent SSR. Others found an association between disease severity and SSR (13). Autonomic failure might lead respirator dependent patients to circulatory collapse or sudden death. Hence, assessment of autonomic failure is important from a management perspective. Moreover, very few studies have explored the association between autonomic dysfunction and ALS in low resource settings such as Bangladesh. Bangladesh is a densely populated South Asian country that harbors an ethnically diverse group of mostly brown people. Studies have shown that there are racial differences in sympathetic nervous system indicators (14).

Hence, exploring autonomic dysfunction in ALS patients in Bangladesh could also generate information from the perspective of South Asian ethnicity. Therefore, we aimed to study the association between autonomic dysfunction measured by SSR, and ALS, in a tertiary care hospital in Bangladesh.

Methods

Study Participants and Settings

This case-control study was carried out between 2018 to 2019 in the Department of Neurology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Thirty-five ALS patients with no family history of ALS were enrolled as cases according to the revised El Escorial diagnostic criteria (15). The sample size was determined using the following formula:

$$N = \left[\frac{Z\alpha\sqrt{2p(100-p2)} + Z\beta\sqrt{p1(100-p1)+p2(100-p2)}}{(p1-p2)}\right]^2$$

Here: N=Sample size of each group; Zα=1.96 (Z value of standard normal distribution at 95% confidence level); Zβ=1.28 (Z value of standard normal distribution at 90% power); p1= Anticipated probability of exposer among case = 40% (13); p2= Anticipated probability of exposer among control = 0% (13); P=(p1- p2)/2. With this formula, sample size, N=22.

A total of 35 patients with ALS fulfilled the inclusion criteria during our study period and were included as cases. Among these cases, 11 were definite ALS, 10 clinically probable and 14 laboratory supported ALS cases. Patients with ALS who had any of the following characteristics or comorbidities were excluded: age >60 years, multiple system atrophy, Parkinson's disease or other neurodegenerative disorders, pure autonomic failure, multiple sclerosis, history of neck or spinal trauma, critical illness (acute MI, stroke, respiratory failure & heart failure), systemic conditions causing autonomic disturbance (DM, CKD), scleroderma, Sjógren disease, any form of neuropathy (diabetic neuropathy, Guillain-Barré Syndrome, hereditary motor and sensory neuropathy, chronic inflammatory demyelinating polyneuropathy), those taking medications causing autonomic disturbances or that could influence the SSR, patients with an

abnormal sensory response in a nerve conduction study, and patients unwilling to participate in the study. SSR is ordinarily present in both hands and feet under the age of 60 years, but it usually decreases in subjects older than 60 years (16). A detailed clinical history was taken, and relevant bedside examinations were performed to exclude autonomic involvement. None of the patients had complaints suggesting autonomic disturbances such as palpitation, postural dizziness, bowel or bladder disturbances, sexual dysfunction, dryness of mouth or skin, and hyperhidrosis. However, patients with bulbar palsy had hypersalivation. On clinical examinations, none of our cases had tachycardia, postural hypotension, or pupillary abnormalities. An equal number of age- and sex-matched (via frequency-matching) healthy volunteers were registered as the control. All participants underwent an assessment of SSR in the electrophysiology lab of the Department of Neurology, BSMMU.

Study Procedure

Data Collection Instrument

Data were collected using a preformed structured questionnaire through face-to-face interviews with the patient and/or their attendant, and through careful physical examination. The questionnaire included demographic variables, including age and sex, the presenting complaints of the patient and details of neurological examination findings, relevant data to exclude other differentials, types of ALS according to El Escorial diagnostic criteria, duration of ALS, severity of the disease, findings of the nerve conduction study, and SSR. All patients who met the inclusion criteria were enrolled, regardless of the duration of their disease. Patients with ALS were divided into different groups on the basis of the duration of their disease, ranging from 1 to 6 months, 7 to 12 months, 13 to 18 months, and over 18 months. Some newly diagnosed patients with a disease duration of less than 6 months underwent diagnostic EMG and SSR in the same settings. Other diagnosed patients with a disease duration of several months or years who came for follow-up underwent SSR for the study purpose.

Functional Assessment of Patients

The involved anatomical sites and clinical manifestations of autonomic dysfunction were identified by interviewing the cases and the ALS Functional Rating Scale-Revised (ALSFRS-R) was used to assess the patients' functional status (17). On the basis of this scale, the functional severity of the disease was categorized as follows: mild (>40), moderate (39–30), severe (<30), and advanced (<20). We utilized King's ALS clinical staging system to determine the clinical severity of the disease: Stage 1 indicates the involvement of a single region, Stage 2 when two regions are involved, Stage 3 when three regions are involved, and Stage 4 when the patients have bulbar or respiratory involvement (18).

Assessment of Sympathetic Skin Response

SSR assessment was done using the NIHON KOHDEN Neuropack MEB-9400 S1 Series EMG/NCV/EP Measuring System. A conventional nerve conduction study of the median, ulnar, common peroneal, tibial, and sural nerves was done initially. The ambient room temperature was maintained between 22–24°C. We measured SSR in the supine position. Before recording SSR, the limbs were warmed to prevent hypothermia. The electrical stimulus was applied as a single square pulse, 0.1–0.2 MSec in duration, delivered randomly and with a minimal interstimulus interval >30 seconds. The stimulus intensity was between 10 and 30 mA. We measured the latency and amplitude of SSR in all four limbs by placing surface electrodes on the palm and sole, and administering electrical stimuli along the median nerve in the upper limbs and the tibial nerve in the lower limbs (10). The SSR was recorded from both sides if both sides were equally affected, and the best response was considered for analysis. If only one side was affected, the response was recorded from that side. In the case

of asymmetrical involvement, the SSR was recorded from the more affected limb. We measured the latency from the onset of the stimulus artifact to the first deflection from baseline. The height of the wave from baseline to the peak of the first positive or negative deflection was recorded as the amplitude (Figure 1, 2, 3). The normal mean onset latency and amplitude of SSR are 1480±80 millisecond (MSec) and 444±167 microvolt (μV) for the hands; 2060±93 MSec and 203±87.4 μV for the feet (19). An absent response was recorded if no reproducible deflection was found after at least three stimulations. Prolonged latency (delayed SSR) or an absent response was considered abnormal SSR.

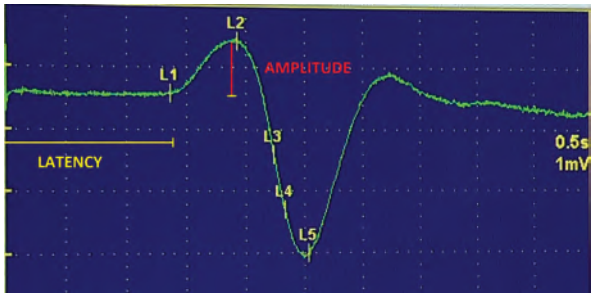

Figure 1. Normal SSR in the upper limb (Sensitivity 1 mV on the vertical axis and 0.5 seconds on the horizontal axis). The horizontal yellow line indicates the latency and the red vertical line indicates the amplitude.

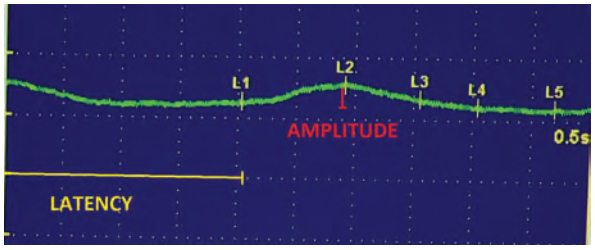

Figure 2. Normal SSR in the lower limb (Sensitivity 1 mV on the vertical axis and 0.5 seconds on the horizontal axis). The horizontal yellow line indicates the latency and the red vertical line indicates the amplitude.

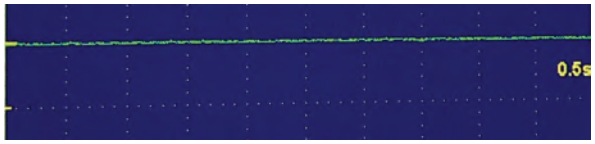

Figure 3. Absent SSR in the lower limb of an ALS patient (Sensitivity 1 mV on the vertical axis and 0.5 seconds on the horizontal axis).

Ethical Considerations

Ethical clearance for the study was given by the Institutional Review Board (IRB), Bangabandhu Sheikh Mujib Medical University (BSMMU) (IRB Number: BSMMU/2018/6176). All the procedures were conducted according to the Declaration of Helsinki. Informed written consent was taken from each patient or their attendant before inclusion.

Statistical Analysis

Both descriptive and analytic statistics were carried out. Data were presented as frequency (percentage) and mean ± standard deviation (SD) for categorical and continuous variables, respectively. Distribution of the quantitative variables were checked using a histogram and the Shapiro-Wilk test. For analytic statistics, the Chi-square test, Fisher's exact test, the independent samples t-test, and the Mann-Whitney U test were used where appropriate. SSR latency and amplitude were compared between ALS patients and control subjects using the Mann-Whitney U test as the data were not normally distributed. Among the ALS patients, the relationship between SSR and the predominantly involved site (limb or bulbar), disease severity, and disease duration were analyzed using the Chi-square test or Fisher's exact test. The Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., Armonk, NY, USA) was used for data analysis. A P-value of ≤ 0.05 was considered significant.

Results

Thirty-five patients with ALS aged 16–60 years, and thirty-five age- and sex-matched healthy controls were included. The mean age of the cases and controls was 37.71±15.02 and 38.43±11.22 years, respectively. The majority of cases were aged below 30 years (37.1%), and the majority of controls belonged to the 31–50 year age group (51.4%), however, the difference was not statistically significant (P=0.341). Out of thirty-five cases, 28 (80%) were

male, and seven (20%) were female, whereas in the control group, 30 (85.7%) were male, and five (14.3%) were female (P=0.526) (Figure 4). The male-female ratios of the cases and the control group were 4:1 and 6:1, respectively.

Table 1 describes the clinical characteristics of ALS patients included in the study. The majority of the patients had developed ALS over a period of 1-6 months (42.9%). All four limbs were affected by wasting and weakness in 60% of patients. None of the patients had any features of autonomic nervous system involvement except hypersalivation (31.4%). The majority of the patients had a mild disease (57.1%), followed by 37.1% and 5.8% having a moderate and severe disease, respectively. None of the patients had the advanced stage of the disease.

Out of 35 cases, SSR was abnormal in the upper limbs of 17 (48.6 %) persons. Among them SSR was absent in six (17.1%) cases, and latency was prolonged or SSR was delayed in 11 (31.4%) cases. Eighteen (51.4%) cases had normal SSR. Among the control population, all had a normal SSR. The difference between cases and controls was statistically significant (P-value <0.001). In the lower limbs, SSR was abnormal in 33 (94.3%) persons. It was absent in 20 (57.1%) and delayed in 13 (37.1%) cases. A normal response was found in only two (5.7%) cases. All of the control samples (N=35; 100%) had normal SSR. The difference between cases and controls was statistically significant (P-value <0.001). The median latency (IQR) was statistically significantly higher and the median amplitude (IQR) was statistically significantly lower in both limbs of the cases compared to the controls (P<0.001 for all). See Table 2 for details.

The SSR was delayed or absent in the upper limbs of 27.3% of cases (each) with bulbar palsy and 33.3% and 12.5% of cases without bulbar palsy, respectively. However, the difference was not statistically significant (P=0.625). On the other hand, a significantly higher proportion of cases

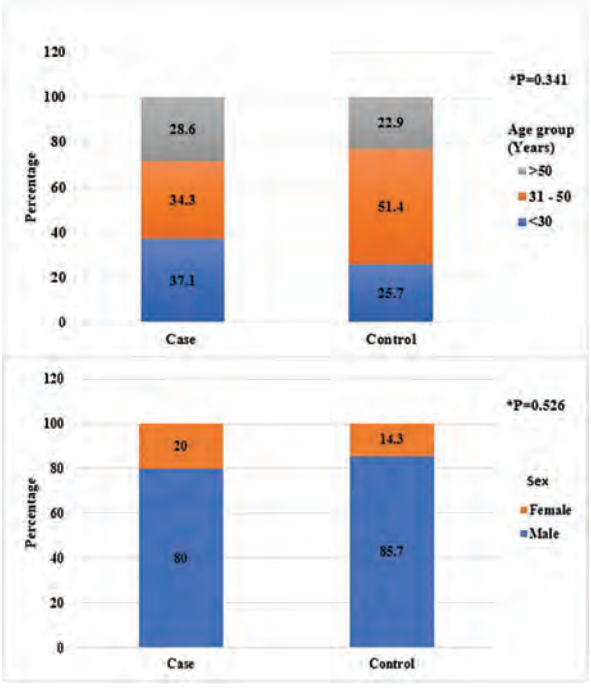

Figure 4. Distribution of case and control by age and sex; *P-value was determined by Chi-square test.

Table 1. Clinical Characteristics of the ALS Patients (N=35)

Clinical characteristics	N (%)
Disease Duration (Months)	
1-6	15 (42.9)
7-12	12 (34.3)
13-18	2 (5.7)
>18	6 (17.1)
Limb wasting and weakness	
All four limbs	21 (60.0)
Both upper limbs	8 (22.8)
Both lower limbs	3 (8.6)
Single upper limb (right)	3 (8.6)
Bulbar palsy (present)	11 (31.4)
Features of ANS involvement	
Hypersalivation	11 (31.4)
Others*	0 (0)
Functional Severity of ALS†	
Mild (>40)	20 (57.1)
Moderate (30-39)	13 (37.1)
Severe (<30)	2 (5.7)
Clinical Severity of ALS‡	
Stage 2	19 (54.3)
Stage 3	4 (11.4)
Stage 4	12 (34.3)

ALS=Amyotrophic Lateral Sclerosis; ANS=Autonomic Nervous System; *Other features of ANS involvement including dry mouth, postural hypotension, and sweating abnormality; †As determined by ALS Functional Rating Scale-Revised (ALFRS-R) (17); ‡As determined by KING's ALS clinical staging (18).

with bulbar palsy had abnormal SSR (9.1% absent, and 81.8% delayed) in the lower limbs compared to cases without bulbar palsy (50% delayed and 45.8% absent, P=0.042) (Table 3).

The distribution of SSR responses was statistically similar across the severity categories of ALS and disease duration for both limbs (P>0.05) (Table 4, 5, 6).

Table 2. Comparison of Sympathetic Skin Response, Its Latency, and Amplitude between Cases and Controls

Sympathetic skin response	Categories	Case (N=35)	Control (N=35)	P-value
Upper limbs; N (%)	Normal	18 (51.4)	35 (100.0)	<0.001*
	Delayed	11 (31.4)	0 (0.0)	
	Absent	6 (17.1)	0 (0.0)	
Lower limbs; N (%)	Normal	2 (5.7)	35 (100.0)	<0.001*
	Delayed	13 (37.1)	0 (0.0)	
	Absent	20 (57.1)	0 (0.0)	
Latency (MSec); Median (IQR)	Upper limbs	1490 (1345–1692)	1175 (1060 –1330)	<0.001†
	Lower limbs	2330 (2195–2880)	1520 (1380–1570)	<0.001†
Amplitude (mV); Median (IQR)	Upper limbs	0.66 (0.24–1.37)	3.63 (3.25–3.80)	<0.001†
	Lower limbs	0.47 (0.18–0.79)	1.54 (1.45–1.76)	<0.001†

IQR=Interquartile range; MSec=Milliseconds; mV=Millivolts; *Chi-square test; †Mann-Whitney U test.

Table 3. Association of SSR with Bulbar Palsy Among Cases (N=35)

SSR	Bulbar palsy		P-value*
	Present (N=11; (N %)	Absent (N=24; (N %)	
Upper limbs			
Normal	5 (45.5)	13 (54.2)	0.625
Delayed	3 (27.3)	8 (33.3)	
Absent	3 (27.3)	3 (12.5)	
Lower limbs			
Normal	1 (9.1)	1 (4.2)	0.042
Delayed	1 (9.1)	12 (50.0)	
Absent	9 (81.8)	11 (45.8)	

SSR=Sympathetic skin response; *Fisher's exact test.

Table 4. Association of SSR with the Severity of ALS (N=35)

SSR	Severity of ALS			P-value*
	Mild (>40) (N=20)	Moderate (30-39) (N=13)	Severe (<30) (N=2)	
	(N (%)	(N (%)	(N (%)	
Upper limbs				
Normal	11 (55.0)	7 (53.8)	0 (0.0)	0.129
Delayed	6 (30.0)	5 (38.5)	0 (0.0)	
Absent	3 (15.0)	1 (7.7)	2 (100.0)	
Lower limbs				
Normal	1 (5.0)	1 (7.7)	0 (0.0)	0.682
Delayed	9 (45.0)	4 (30.8)	0 (0.0)	
Absent	10 (50.0)	8 (61.5)	2 (100.0)	

SSR=Sympathetic skin response; ALS=Amyotrophic lateral sclerosis; *Fisher's exact test.

Table 5. Association of SSR with the KING's ALS Clinical Staging (N=35)

SSR	Severity of ALS			P-value*
	Stage 2 (N=19)	Stage 3 (N=4)	Stage 4 (N=12)	
	N (%)	N (%)	N (%)	
Upper limbs				
Normal	9 (47.4)	3 (75.0)	6 (50.0)	0.843
Delayed	7 (36.8)	1 (25.0)	3 (25.0)	
Absent	3 (15.8)	0 (0.0)	3 (25.0)	
Lower limbs				
Normal	1 (5.3)	0 (0.0)	1 (8.3)	0.051
Delayed	9 (47.4)	3 (75.0)	1 (8.3)	
Absent	9 (47.4)	1 (25.0)	10 (83.3)	

SSR=Sympathetic skin response; ALS=Amyotrophic lateral sclerosis; *Fisher's exact test.

Table 6. Association of SSR with Disease Duration of ALS (N=35)

SSR	Disease duration (months)				P-value*
	(N=15)	7–12 (N=12)	13–18 (N=2)	>18 (N=6)	
	N (%)	N (%)	N (%)	N (%)	
Upper limb					
Normal	7 (46.7)	7 (58.3)	1 (50.0)	3 (50.0)	0.891
Delayed	5 (33.3)	4 (33.3)	0 (0.0)	2 (33.3)	
Absent	3 (20.0)	1 (8.3)	1 (50.0)	1 (16.7)	
Lower limb					
Normal	1 (6.7)	1 (8.3)	0 (0.0)	0 (0.0)	0.945
Delayed	6 (40.0)	3 (25.0)	1 (50.0)	3 (50.0)	
Absent	8 (53.3)	8 (66.7)	1 (50.0)	3 (50.0)	

SSR=Sympathetic skin response; ALS=Amyotrophic lateral sclerosis; *Fisher's exact test.

Discussion

This study aimed to assess autonomic dysfunction in amyotrophic lateral sclerosis patients by testing sympathetic skin response (SSR). SSR is one of the electrophysiological autonomic function tests used to examine autonomic involvement. We found that a large proportion of patients had autonomic nervous system involvement despite the absence of significant clinical features suggestive of autonomic dysfunction.

In our study, the mean age of ALS was found to be lower than in other studies because patients aged 60 years and older were excluded from the study (11, 12). A large-scale population-based study on the epidemiology of ALS patients in Bangladesh is yet to be done. However, in a study of 42 ALS patients, the mean age was reported to be 44.64±16.4 years, which is lower than that of western population-based studies (20), whereas, an Indian study of 1153 ALS patients reported a similar mean age of 46.2±14.1 years (21). To rule out age-related effects on SSR *a priori*, we included only cases and controls less than 60 years of age. So, the mean age of our patients was even less than in previous studies in Bangladesh and India. However, the proportion of male patients was high, reflecting the higher prevalence of ALS among males than females worldwide (22).

The median SSR latency was found to be significantly longer in both limbs of ALS patients compared to the controls. Additionally, SSR amplitude was significantly reduced (or absent responses) in cases compared to the healthy controls. This finding is similar to that of studies conducted by Dettmers et al. (13), Hu et al. (12), and Masur et al. (23), but dissimilar to that of Miscio et al. (24). There are conflicting opinions on whether SSR is a good assessor of autonomic dysfunction in ALS patients. However, the investigation by Oey et al. showed that when several aspects of autonomic dysfunction are considered, the subtle involvement of the autonomic nervous system can be found (25). Therefore, our findings endorse the assertions of autonomic involvement in ALS.

Similar to previous studies, we also noted that delayed or absent SSR was more marked in the lower limbs (12, 13). SSR is length dependent. Hence, a higher frequency of abnormality in the lower limbs is not unusual. Some authors prefer not to consider low amplitude SSR an abnormal response. Vertrugno et al. considered only an absent response as abnormal (10). The reason some authors differ in considering low amplitude abnormal is habituation. With repeated stimuli, the SSR amplitude gradually diminishes (26). However, like Hu et al. (12), we considered increased latency and reduced amplitude of SSR to be abnormal findings. We ensured adequate intervals between stimulations to avoid habituation and to ensure the accuracy of measurements. Moreover, we excluded cases with sensory abnormalities to avoid confusing somatic sensory nerve abnormalities with abnormal sympathetic skin response. As the pathway of SSR involves somatic sensory nerve as the afferent, sensory abnormalities may lead to prolonged latency in SSR. Therefore, it can be argued that the abnormal SSR in our patients was due to autonomic involvement.

We divided our cases according to the anatomical location of the predominant clinical involvement: ALS with bulbar palsy and ALS without bulbar palsy. Interestingly, we found significantly more abnormal SSR in the lower limbs of patients with bulbar palsy compared to patients with predominantly limb involvement. This is opposite to the report by Dettmers et al. (13). More studies are required to draw any conclusions on these associations.

Dettmers et al. demonstrated that SSR was more often absent in the advanced stage of the disease (13). We did not find any statistically significant association between abnormal SSR and the functional or clinical severity of ALS. However, we had only two patients with severe ALS according to the functional severity scale, and four patients with Stage 3 disease according to clinical staging. It would be premature to conclude any association between SSR abnormalities and the severity of the disease. We also did not find any correlation between absent SSR and disease duration. Our finding is supported by the observations by Hu et al. (12) and Masur et al. (23). Nevertheless, more data are needed to rule out or establish any association of SSR with the disease severity or the duration of ALS.

As the afferent pathway in our cases was normal, SSR abnormality in ALS was most likely due to central pathway or sympathetic dysfunction. In most of the previous relevant studies, they found the postganglionic sympathetic pathway was the abnormal linkage in the SSR pathway (12, 13), while others suggested central pathway involvement in addition to the postganglionic sympathetic route (11). In ALS patients with bulbar palsy, the central pathway may play a major role. The specific localization of the involved pathway was beyond the scope of this research. Hence, further studies are recommended.

None of our cases had any clinical feature of autonomic dysfunction except hypersalivation. All our ALS patients with bulbar palsy (N=11) complained of hypersalivation. This prevented us from considering hypersalivation as a symptom of autonomic failure. Previous studies also suggest that abnormal SSR in ALS occurs without clinical expression of autonomic dysfunction (12, 13). Hence, the abnormal SSR among our patients could be an indicator of subclinical autonomic dysfunction.

There are several possible mechanisms behind the autonomic involvement in ALS patients, and

the anterior horn cells, the autonomic nuclei of the spinal cords (intermediolateral column) can be affected by similar mechanisms (27–29). Neuronal loss was found in the spinal cord involving these nuclei. An intracytoplasmic inclusion body was also found inside Onuf's nucleus (30). As contiguous anatomic regions are involved in ALS, neural degeneration may progress to involve the parasympathetic nuclei of the brainstem in patients with bulbar involvement (31). Ultrasonography of the vagus nerve at the level of the thyroid gland revealed atrophy in ALS patients (32). The mechanisms behind autonomic nerve degeneration may be similar to the process causing the death of motor neurons in ALS (6).

Electrochemical skin conductance (33), Quantitative Sudomotor Axon Reflex Test (QSART) (34), ultrasonography of the vagus nerve (8, 9, 32), and skin biopsy (35) are other tests which can be combined with SSR to further confirm autonomic dysfunction in ALS patients. Apart from skin biopsy, the other tests are simple and noninvasive methods. We recommend further study using all these modalities in the same ALS cohort to assess which test is superior in assessing autonomic dysfunction.

Limitations of the Study

Our study had several limitations. The sample size was small. Representation of female participants was low. We evaluated our patients clinically for autonomic dysfunctions by using a questionnaire focusing on symptoms and bedside signs such as postural hypotension. Other evaluations of autonomic dysfunction, such as recording changes in heart rate and blood pressure during the Valsalva maneuver, could not be done. We also could not include other electrophysiological tests such as QSART or ultrasonography of the vagus nerve. However, our results add to the evidence that ALS patients might have subclinical autonomic involvement.

Conclusions

Given our study findings, ALS could be considered a multisystem disease. In addition to motor system involvement, ALS patients might have subclinical autonomic involvement. However, more studies are required to establish any association of the frequency of abnormal SSR with disease severity and duration. Abnormal SSR may have a prognostic value in ALS patients, as we had more abnormal findings in patients with bulbar involvement.

What Is Already Known on This Topic:
Previously ALS and other MNDs were considered to be diseases involving only the motor system. Later, some studies suggested they also involve the autonomic nervous system. Autonomic dysfunction in ALS patients can be assessed by both clinical findings and investigations. One of these assessment tools is SSR. Abnormal SSR in ALS patients is suggestive of autonomic dysfunction. In some studies, there was also an association between abnormal SSR and disease severity and duration.

What This Study Adds:
We found abnormal SSR in ALS patients without any clinical features of autonomic dysfunction. Abnormal SSR in ALS patients may suggest subclinical autonomic dysfunction in South Asian people. There is also a possible association between bulbar palsy and abnormal SSR, which may indicate the prognostic significance of abnormal SSR in ALS patients.

Authors' Contributions: Conception and design: MH, SMA and HZR; Acquisition, analysis and interpretation of data: MH, SMA, HZR, MASK and MRH; Drafting the article: MH, MASK and MRH; Revising it critically for important intellectual content: MASK and MRH; Approved final version of the manuscript: MH, MASK and MRH.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Prejudice and Fear as Influences in Relation to a Successful Organ Donation – Experiences of Immigrants Living in Sweden

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Abstract

Objectives. The purpose of this study was to determine whether fear and prejudice in relation to organ donation and the transplantation of organs may influence the decision to become an organ donor. **Materials and Methods.** Data were collected through four group interviews using open-ended questions and qualitative content analysis. Forty participants, 16 males and 24 females from seven countries, participated in the focus group interviews. **Results.** The analysis resulted in three main categories, and nine subcategories. Fears and prejudice caused by tradition and customs, approval of organ donation by family members, perception of the body as a gift from parents, the influence of religious leaders, knowledge about the religious understanding of organ donation, influence of social ambience on respondents, knowledge of the donation process in the healthcare system, including knowing about life after eventual organ donation, were some of predictors in the decision to agree to organ donation. **Conclusion.** More education on the factors that influence organ donation, more information in schools, health institutions and through the media, as well as more research with the aim of "dispelling" fears and prejudice about organ donation would significantly improve the current situation and result in a larger number of potential organ donors.

Key Words: Prejudice ▪ Fear ▪ Influence ▪ Immigrants ▪ Organ Donation.

Introduction

More than 15 million people aged between 30 and 70 years die of non-infectious diseases, every year. About 85% of these "early" deaths occur in low- and moderate-income countries (1). Changing population demographics and an increasing prevalence of risk factors have contributed to the growing demand for organ replacement therapies. The transplantation of organs (TO) and organ donation (OD) are therefore the only option for the restoration of organ function and the prevention of early death for many patients (2). TO and DO restore not only organ function but also quality of life. In different countries in Europe and around the world, different factors, including owning or not owning donor cards, influence the decision by individuals to be or not to be donors of their organs. The reduced availability of organs and increased difficulty distributing them to patients on the waiting list, the co-modification of organ transplantation, the exploitation of potential donors and the determination of the perception of death have raised ethical and societal questions (3). Religion and religious beliefs may influence the decision to donate organs. In Buddhism and Hinduism, organ donation is seen as an act of generosity, while in Catholicism the leading belief is

that people should help others who are in need for help (4). Attitudes in Judaism vary because of the dilemma between saving lives and benefiting from the dead (5). Even in Islam, there are different views about the transplantation of organs and organ donation (6, 7). Different cultural beliefs may influence organ donation (8). Knowledge of and attitudes towards donation may also affect organ donation (9). Different ages, gender, motivation and the quantity of received information about organ donation, the educational level of informants, geographical location and changing the country of residence may affect the decision to become a donor (10-14). All the above-mentioned factors and all the referenced studies indicate more or less fear and prejudice as factors that can directly or indirectly influence individuals to decide to donate or not. In all these studies, we can read sporadically that these are also the two factors that can influence organ donation. However, there is no study in the world that treats and examines only the two factors that influence the decision regarding organ donation. No study in Sweden has been carried out to assess immigrants' views of fear and prejudice as factors affecting the decision to donate. The author's hypothesis is that different fears and prejudice about organ donation are crucial factors in the decision regarding the transplantation of organs and organ donation.

The present study aimed to determine whether and, to what extent, fear and prejudice relating to organ donation and the transplantation of organs may influence the decision to become an organ donor.

Methods

Design and Participants

The study was designed as a qualitative study using data from interviews with participants from Bosnia and Herzegovina, Macedonia, Turkey, Lebanon, Slovenia, Croatia and Kosovo. The data were collected through four focus group interviews (15). The inclusion criteria were participants from the respective countries, more than 20 years of age, who had lived in Sweden for more than 10 years. Forty-nine participants took a class on their religion and organ donation. The interview was organised by the Bosnian and Somalian Association in Gothenburg, from June 2022 to February 2023. The four interviews took place in groups the following year, with about one interview a month. Forty participants participated in the interviews, 24 women and 16 men, aged between 40 and 83 years (mean 61.5 years). The men were aged between 46 and 74 (mean 59.0 years) and the women between 41 and 70 (mean 55.5 years). The interviews and all the communications were held in the Bosnian and Swedish languages. The interview groups contained individuals of different ethnic origins, different genders, and different ages. The demographic and clinical characteristics of the informants are shown in Table 1.

Data Collection

Data were collected through group interviews conducted by the first author (FK), using individualised open-ended questions, following an interview guide inspired by Kvale (1997) (16). They began with small talk. The opening questions were "What do you know about the factors impacting organ donation?", "Would you consider donating your own organ or organs to other people?" and "Do you have fear about the organ donation process?" and "What do you think about prejudice in organ donation?". The initial questions were supplemented with other short questions, such as "Could you please tell me more about that?" and "What do you mean by that?". All contact with the participants was organised in collaboration with a key person in a Bosnia and Herzegovina and Somalia Association in the western part of Sweden. Participants who participated in the interview and met the inclusion criteria were asked to participate in the study. When the key person had recruited enough participants, the author of the study was contacted, and the interview was arranged. Printed information about the aim and background of the study was distributed to the participants and repeated to them orally before

Table 1. Demographics and Clinical Characteristics of the Informants

Characteristics	Number
Sex	
Male	16
Female	24
Total	40
Educational level	
Elementary school	35
High school	3
University	2
Total	40
Age (y)	
40-50	8
51-60	12
61-70	6
71-80	7
≥80	7
Total	40
Countries of birth	
Bosnia and Herzegovina	8
Kosovo	5
Lebanon	5
North Macedonia	7
Turkey	6
Croatia	5
Slovenia	4
Total	40
Religion	
Islam	34
Christian Orthodox	2
Catholics	2
Other	2
Total	40

the interview. The interviews were carried out in groups and held in the facilities of the Bosnian and Somalian Association. The interviews were carried out in Bosnian and Swedish by the author of the study, who is bilingual. Some younger participants chose to speak Swedish. All the interviews were therefore first translated into Swedish by the first author (FK), after which a professional translator checked the translation. The interviewer only interrupted to ask questions or to follow up on the information given. All the participants gave their signed informed consent before the interviews. The interviews lasted between 58 and 120 minutes, with an average of 89 minutes, and were taped and transcribed verbally.

Statistical Analyses

The qualitative content analysis method, in accordance with Graneheim and Lundman (2004), was chosen for the analysis and interpretation of the collected data. This method is suitable for the analysis of qualitative data because, using this method, the researcher is able to condense a large amount of data into a small number of codes, subcategories, categories and themes (17). The author conducted a manifest analysis of the text. The transcripts were read carefully in order to identify the informants' experiences and conceptions. The analysis then proceeded by extracting meaningful units, consisting of one or several words, sentences, or paragraphs, containing aspects related to each other and addressing a specific topic in the material. Meaningful units, related to each other through their content and context, were then abstracted and grouped together into a condensed meaningful unit, with a description close to the original text. The condensed text was further abstracted and labelled with a code. Codes that addressed similar issues were then grouped together, resulting in subcategories. Subcategories that focused on the same problem were brought together, in order to create more extensive conceptions, which addressed an obvious issue (Graneheim and Lundman 2004) (17). The results are presented with direct quotations from the interviews (Table 2).

Research Rigour

According to the criteria for research rigour there is a difference regarding the criteria for quantitative research and qualitative research. Based on this context the criterias for our study, which is a qualitative research study, are transferability, credibility, confirmability and dependability. These

criterias correspond to both internal and external validity as well as objectivity and reliability. These are notions applied in quantitative methods (18). The nature of the present study and its topic, methodology, aims and supposition did not correspond to the criteria regarding quantitative methods. It is therefore on this note the idea behind the development of a specific criteria for qualitative methods is based on. Reliability implies that the same result should be accomplished regardless of who accomplishes the test. In qualitative research, there is a slight impossibility for two researchers, with a recurring study, to reach the same result because of different understandings. However, there is a possibility for them to reach approaching experiences. According to the research rigour, credibility is a reflection of the researchers ability to present and communicate the knowledge and its validity. Factors such as sampling, analysis of methods, the pre-understanding of the researcher and description of the data collection have an influence on the data and its credibility. The transferability in a qualitative study is based on the extent the results are possible to transfer to other contexts (19). It is important that the results are critically evaluated in a similar field and in regard to previous studies. The analysing of text was performed with attention to unitizing – segmenting the texts for analysis – sampling- selecting an appropriate collection of units to analyse. Reliability – different researchers making codes consistenly, and Validity – using a coding scheme that adequately represents the specified phenomena (18, 19).

Ethics Statement

Since there was no physical intervention and no information on individual health issues was involved in the study, there was no need to involve the ethical board, in accordance with Swedish Health and Medical Services Act (2017) (20), and according to Act on ethical review of research involving human subjects (21). The World Medical Association Declaration of Helsinki (1964) (22), was followed carefully. The informants' identities were protected, i.e. their names and personal identity numbers were not stated in the recordings or any publications. The audiotapes used for the interviews were stored in a locked safe at the hospital. The identity of the participants could therefore not be traced. The study information given to the participants included its voluntary nature and the fact that they could withdraw at any time without incurring penalties or losing access to services.

Results

The analysis of the text resulted in three main categories and nine subcategories, based on the participants' description of their thoughts about fear and prejudice as influencing factors regarding OD. The categories, together with the subcategories, are presented in Table 2. The categories were: insufficient information, religious influences, socio-cultural influences and cost related issues.

Table 2. Overview of the Theme, Categories and Subcategories

Categories	Subcategories	Theme
Insufficient information	Knowledge about donation process	_
	Fear about life after donation process	_
Religious influences	Influence of religious leaders	_
	Influence of knowledge in religion	Prejudice and fear as predictors in a successful organdonation
Socio-cultural influences	Influence from family members	_
	The gift from the parents	_
	Influence of the social ambience	_
Cost related issues	Knowledge about fees in donation process	_

Insufficient Information

During the entire interview, it became clear that that all the participants in the study are only physically in Sweden, but that they are mentally and with all their hearts in their home countries. Ignorance and lack of information about how an organ donation process works, how the health system works, the payment obligations during the process, the duties and rights of the person who donates his/her organs, as well as what happens after the organ donation is complete, were just some of the questions about which the participants in the study had no idea. Fears and prejudice weighed most heavily and were most frequently expressed in this section.

Knowledge of Donation Process

Knowledge relating to the process of organ donation was scarce among the majority of participants. Most of them were ashamed to talk about the fact that they do not know how an organ donation takes place. In this case, their knowledge and information were based on the stories of acquaintances and family, on the retelling of various fears, as well as on the basis of various prejudices.

"I heard that, a long time ago, a guy applied to donate a kidney and they removed all the organs he could donate at the hospital."

"I heard that, if you get hurt, nobody wants to save you because they need your organs."

"I'm afraid of being in hospital."

Fear about Life after Transplantation

Thinking about the future, thinking about the existence of descendants, as well as about life after organ donation was present in a few participants. Again, there was ignorance, a lack of knowledge, as well as distrust in the healthcare system.

"After the operation, you have to be on sick leave for a long time and I don't have the funds for that"

"I heard that the operation has to be repeated several times… more absence from work… more risk of dismissal. No thanks."

Religious Influences

Almost all the participants regarded themselves as religious and the influence of religion regarding organ donation was strong. People who preached religion, knowledge of the connection between religion and organ donation, as well as influence from the people around them, were strongly emphasised by all the participants in the study. Prejudice and fear were present here.

Influence of Religious Leaders

From the point of view of blindly listening to everything a religious leader says and blindly believing it, thoughts between the participants were shared. While some participants believed everything their leader said, there were some who took this with a "pinch of salt" and something that needed to be checked carefully. While some did not want to disappoint their leaders, there were others who were afraid of what their leaders would think of them.

"I don't know how my leader would react, if I said something against him."

"Once, what my leader said about organ donation wasn't true, but I didn't dare say anything."

Influence of Knowledge in Religion

The same discussion among the participants was about whether religion allows organ donation. On the one hand, there were those who believed that religion allows organ donation, but not its abuse. On the other hand, there were people who strictly believed that religion does not allow organ donation. Fears of the thought of making a mistake, of hurting their religion, as well as the fact that prejudice was an integral part of this life were present in all the participants in the study.

"I'm afraid to think about organ donation because my religion doesn't allow it."

"I heard that, if organs are donated, you have no place in the other world, in your religion."

"All religions allow organ donation, but I'm afraid."

Socio - Cultural Influences

According to participants in this study, cultural and culturological factors linked to fear and prejudice in relation to decisions to donate their organs were multifaceted. Despite the fact that the majority of them have lived in Sweden for more than 20 years, their traditions and customs from their respective countries were so strong that it felt as though all the participants were "imprisoned by" them. The influence of the family, who had to approve every part of the donation process, was no less important. The participants who came from non-European countries perceived their body as a gift from their parents. In all their narratives, fear and prejudice were interwoven, so that, if there was more fear, then there was less prejudice and vice versa.

Influence of Family Members

Connection to the family and family members on the issue of organ donation was equally strong. No matter how urgently the organ needs to be fixed and how urgently the person needs it, the family must approve this. Participants stated that it sometimes happened that the family approved the donation, but that it was usually too late. Many times, they did not even dare to ask about organ donation.

"Once we needed a kidney for my brother, but we didn't ask for a donor… we were afraid of the reaction."

"If you are not liked by the family, then you have no place in the next – real life."

A Gift from the Parents

All the participants placed their parents next to God. The will of the parents was their own, they showed a great deal of respect to their parents, they did everything to make their parents proud and they thought that their body and all their organs were created by God and given by their parents. Fear and prejudice were also present here.

"I don't have the right to give my organs to others because I don't own them."

"I heard that a person donated his organs and dreamed about his parents for many years."

Influence of the Social Ambience

All the participants in the study felt uncomfortable when it came time to talking about their friends, acquaintances, neighbours and work colleagues and about donating organs. Their thoughts on organ donation slowed down the way their surroundings functioned, because they did not know how the people around them (their environment) would react if they decided to donate their organs.

"I don't dare to think about how the people I know would react if they heard about my possible plans for donation."

Cost Related Issues

An additional burden, additional fears and the awakening of prejudice were also caused by daily events related to warfare, high living costs and increasing living standards,

Knowledge about Fees in Donation Process

In this subcategori, the majority of participants were convinced that they were obliged to pay the price of organ donation. Ignorance of the way the health system functions triggered additional fears among all participants.

"I am afraid that, if I decide to donate organs and if something happens to me, my family will have to bear all the costs."

"Generally, the situation in the world is difficult and I don't need additional expenses."

Discussion

The present study is the first study in Sweden and in the world to investigates only the relationship between fear and prejudice as a direct influence on the decision relating to the transplantation of organs and organ donation. This is also the first study to include informants from seven different countries and two different continents. In qualitative studies that are based on interviews where the goal is to interpret texts at different levels, a qualitative content analysis is a suitable analysis

method (17). The authors considered this appropriate in order to illuminate the purpose and see it from its parts and as a whole.

The goal was to get a result that is based on an analysis that is possible to follow by being transparent but that is still abstract and innovative. The choice to proceed with a theme was then made. By making the analysis process joint, the risk of the material that responded to the purpose getting lost was eliminated. To further eliminate this, the codes were compared against the meaning units to ensure that the meaning was not lost (17). The results of the study are based on the characteristics of the participants – one group of 40 participants, of which 24 were women, and 16 of them were males. The majority of them had completed an elementary-school education, most belonged to the religion of Islam, and were between 50-60 years old. All of them spoke Swedish and the participants from the Balkans spoke Bosnian. The hypothesis the author puts forward in the introduction to the study – that different fears and prejudice about organ donation are crucial factors in the decision to transplant organs and organ donation – proved to be more than accurate in the present study. Regardless of the dialogue segment and the part of the interview, fears and prejudices in organ donation were visible among respondents in the study. Based on all the conducted interviews, the authors of the study have the impression that the participants in this study are somehow "stuck" in their thinking about anything other than their fears and prejudice.

On top of all the other daily obligations and burdens, "shackles" from the insufficient information about organ donation, the influence of religion and knowledge of the attitude of religion regarding organ donation, as well as the sociocultural influences in decision to organ donation and cost related issues, prevented the participants in this study from thinking at all. On the issue of organ donation and transplantation, it appears that the participants in this study simply do not have that subject in their lives. The result of the present study showed that the majority of the participants had not reached the level of thinking about organ donation. In the part of the interview that talks about the insufficient information about organ donation and the process after the organ donation that can affect the respondents and their decision to donate organs, answers about patriotism and the fact that the majority of the respondents live in Sweden only because the situation in their home countries is bad dominated.

Despite the fact that all the respondents knew the Swedish language and most of them were educated and worked in Sweden, most of the fears and prejudices they expressed during the interview regarding the socioeconomic factors that influence their decision were precisely caused by ignorance regarding the functioning of the process, the organization during organ donation as well as ignorance of the organization of the health care system of the state where they had been living for the last 20 years or more. Perhaps the answer to that question should be searched for in the very pronounced patriotism that all the respondents visibly displayed. The first fears and prejudices regarding the information and knowledge that hinder organ donation were precisely the ignorance about the donation process as well as the functioning of the healthcare system. This supports the findings of other studies around the world, where knowledge level has been shown to predict people's attitude towards OD. Those with more knowledge were more likely to participate in OD (23). The authors found that people looked at various magazines about religion and health and thus gained additional knowledge, watching television and using the internet also helped study respondents to gain more knowledge. In another study, it was initially shown that respondents know a lot about OD (11, 24-26). It is good for people to find information about both OD and the healthcare system themselves. Ignorance and lack of interest, as well as fears and prejudices about organ donation were a bad combination for the decision to donate organs among all respondents.

The result of our study also shows that ignorance of the functioning of the healthcare system, and the process of organ donation leads to ignorance about the cost of organ donation in Sweden,

as well as the fact that patients in Sweden do not pay for surgery (11). The respondents of the study did not show any more knowledge about the healthcare system and the condition of possible donors after the operative process. The combination of fears and prejudices of all respondents made the situation only worse. One study from Denemark showed that the use of the healthcare system was caused by the economic situation, the level of education, the level of income, as well as the fact that the more diseases the patients had, the more they seeked and used the health system (27). Fear and prejudice after possible organ donation were also present in several participants of the study. Similar results to the results of our study were shown in other studies in patients who underwent kidney transplantation and who expressed similar fears and concerns. Study participants were concerned about the safety of the surgical transplant procedure, as well as fear of possible postoperative complications. For patients who were far from hospitals, fears were most often about insufficient and irregular care, which could lead to additional health complications of the subjects (28). This included a distinct concern about kidney transplantation failure, leading to a return to dialysis and significant time spent away from home trying to find another donor (28-30).

A large number of participants in the presented study belonged to the Islamic religion; their knowledge of Islam's position regarding organ donation was thin and was based on the teachings of one imam. Sometimes that knowledge was good and sometimes it was at a low level. Most of the participants in the presented study were of the opinion that Islam as a religion opposes organ donation. An additional barrier was the influence of the environment on people's thinking and decisions about organ donation. In a similar study (31), it emerged that Islam as a faith allows organ donation, but few Muslims were aware of this. Muslims in the study want clear messages from their religious leader. This would make them less uncertain about their position, as they hesitated to take a position until they received the go-ahead from their leader. Coming to the next life intact with one's body whole, not mixing different organs with different bodies and preferably donating one's organs to those who belonged to the same religion were also views that emerged in the study (32).

Most of the participants in the study were positive about organ donation, but they did not know their religion's point of view (31, 32). Relgion is not the only factor having an impact on people's choice to donate. Socio-cultural influences, tradition and customs, influence from the family and the perception that they do not own their body but that it is a gift from their parents also contributes to their final stand regarding the question of donation. A study along the same lines as the present one, which dealt with Chinese people living in Canada, showed that culture, traditions and customs were very important in the decisions about organ donation. Talking about death was an unwelcome topic, which in turn caused the participants to have difficulty talking about organ donation (33). A similar study found that older Asians living with their old traditions and customs found it difficult to think about and donate their organs after death. The younger generations, on the other hand, who had been affected and influenced by western culture, had changed their opinion and were more positive about organ donation. This did not mean, however, that they were prepared to forget and bury the old traditions and customs (34). Unfortunately, this is not the case in our study with participants from several countries and two different continents, with life in the West for more than 20 years but with retained cultural and cultural customs. Some cultures perceive organ donation as harming the body and that the body and all the organs are gifts from the parents and ancestors (35).

On the other hand, some traditions believe that life is a gift and gifts should be given, which was a positive attitude towards organ donation (34). Fear of how the family and family members would react to the need for a donor or organ donation was another obstacle for most participants when it came to thinking about organ donation. The fears were so great that organ donation was not even thought about, instead the person who needed the organ surrendered to his fate. Similarities could also be

found regarding donating an organ to someone else. The fear in searching for a potential organ donor or deciding to donate personal organs was shown in another study. Potential recipients reported particular difficulties in asking family or others to be evaluated as directed kidney donors. Finding a donor was more challenging when there was a high level of shared medical comorbidity in families and communities that increased the expected risk to the donor. This most often led to the decision not to donate organs nor receive organs from other people (36). In a study, in which 499 teachers from Bosnia and Herzegovina participated, the majority of them clearly presented positive thoughts about organ donation. The teachers came from the three major religions, Orthodox, Catholicism and Islam, and would accept an organ from both living and deceased donors. However, there was a difference between the religious groups regarding this issue (P=0.063). Some also stated that they would donate from a deceased member of the family, while others were uncertain about this type of donation. There was no significant difference between the religious groups that were questioned (P=0.769). Regarding the question of who they would donate to, the majority answered that they would donate to a relative, while only a few said that they would donate to someone they did not know. A significant difference between the groups could be noted here (P=0.002) (10). Unfortunately, the result of that study contradicts the result of the presented study, because the study participants, due to various fears and prejudices, did not reach the stage of thinking about organ donation and it was impossible to think about the process. Thoughts about the future, about the time after the operation and about possible complications, were followed by fear that the family will bear costs. Economic situation globally made matters even worse. A similar study where authors of the study hypothesized that African American (AA) living kidney donors have a greater risk of kidney failure than European American donors. Apolipoprotein L1 (APOL1) gene variants in AA may be associated with this difference. Semistructured interviews assessed attitudes about APOL1 gene testing, willingness to undergo APOL1 testing, hypothetical donation decisions with two APOL1 variants, and demographics. Participants were concerned about insurance coverage and costs of APOL1 testing and feared that APOL1 genetic test results could discriminate against AA (37).

Every society and social community must work to ensure that every day there are more organ donations, transplants and therefore more lives saved. However, neither medical progress, nor improved economic growth, nor perfect technological equipment, nor changes in legislation can bring an increased number of organ donations without high social responsibility and a high degree of civic solidarity. The secret of success in organ donation and transplantation is continuous, careful, dosed but honest information to the public and also education of the population.

Study Limitations

The present study has some limitations. The interviews were held in mixed groups, with subjects from seven different countries, two continents and of both genders, which may have made the participants nervous, making it difficult for them to concentrate during the interview and the discussion. Another limitation may be that the interview took place during various activities on the premises of the Bosnian and Somalian Association, so at the time it was very noisy, which caused anger, nervousness and difficulty concentrating for some participants.

Conclusion

The results of the present study show that there are many different opinions that influence participants' decision-making on the subject of organ donation. These views are associated with people's cultural and religious affiliation, level of knowledge, sociocultural influences and how well the discussion within the family on the subject of organ donation works. Today's global geopolitical situation also influenced the participants in their thinking

about organ donation. However, the greatest barrier in the process of starting to think about organ donation was various kinds of fear and prejudice. The healthcare system should work more actively to make information and knowledge on the subject of organ donation more accessible to the population. This may mean that more information in different languages about where different religions stand on the subject of organ donation is presented. It may also mean that the information should have a cultural angle in view of today's multicultural society, which exists in both Sweden and the world as a whole.

What Is Already Known on this Topic:

The transplantation of organs and organ donation are the option for the restoration of organ function and the prevention of early death for many patients. Organ donation restores not only organ function but also quality of life. Different cultural beliefs, knowledge of and attitudes towards donation, ages, gender, motivation, and the quantity of received information about organ donation, the educational level of informants, geographical location and changing the country of residence, and even fear and prejudices may affect the decision to become a donor.

What this Study Adds:

Despite the top scientific and medical achievements in the form of organ donation and transplantation, there are still obstacles and factors that hinder their realization. These factors are associated with people's cultural and religious affiliation, level of knowledge, sociocultural influences and how well the discussion within the family on the subject of organ donation works. Today's global geopolitical situation also influenced the participants in their thinking about organ donation. However, the greatest barrier and brake in the process of starting to think about organ donation was various kinds of fear and prejudice.

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Systematic Review
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An Efficacy and Safety Comparison of Regorafenib and Nivolumab in Unresectable Hepatocellular Cancer Patients: A Systematic Review

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Abstract

Objective. This systematic review aimed to compare the efficacy and safety of regorafenib and nivolumab, two FDA-approved second-line treatments for unresectable Hepatocellular Carcinoma (HCC). **Methods.** Literature comparing the efficacy and safety of regorafenib and nivolumab in unresectable HCC patients was systematically searched across seven databases, including: PubMed, SCOPUS, Cochrane Database of Systematic Reviews, ScienceDirect, EBSCOhost, EMBASE, and ProQuest, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The search was done on April 2nd, 2023. Study quality and risk of bias were assessed using the Agency for Healthcare Research and Quality (AHRQ) and ROBINS-1 tools. The selected studies were included in the qualitative data synthesis. **Results.** Three trials found that HCC patients taking nivolumab had statistically insignificantly longer OS, TTP, and progression-free survival than those on regorafenib. Nivolumab increased ORR, with largely partial responses, and mixed DCR, with little statistical significance. All three studies showed that nivolumab had fewer side effects and improved tolerance. **Discussion.** Three retrospective cohort studies with a total of 383 regorafenib-receiving cohorts and 230 nivolumab-receiving cohorts were included in the qualitative analysis. Nivolumab was found to be superior in regards of longer overall survival, longer time to progression, higher objective response rate, and lower adverse event occurrence. However, statistical significance was not achieved in most of the parameters. **Conclusions.** The use of nivolumab is preferable as the second-line systemic therapy for unresectable HCC. More high-quality studies are urgently needed to generate quantitative analysis, and to encourage the formation of guidelines for second-line systemic therapy.

Key Words: Unresectable Hepatocellular Carcinoma ▪ Regorafenib ▪ Nivolumab.

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide, with an increasing incidence. In 2020, an estimated 905,700 people were diagnosed with, and 830,200 people died from liver cancer globally. The age-standardized incidence for new cases of and deaths from HCC were 9.5 and 8.7 per 100,000 people, respectively. Liver cancer was among the top three causes of cancer deaths, with the number of new cases and deaths expected to increase by 50% by 2040 (1-3). Early diagnosis and tumor staging are key for treatment and prognosis. The Barcelona Clinic Liver Cancer (BCLC) staging system is often used to link tumor features, patient characterization, treatment options, and expected survival. HCC in BCLC class 0 (very early stage) or class A (early stage) is usually eligible for local ablation, resection, and liver transplantation. In BCLC class B (intermediate stage), transarterial chemoembolization (TACE) has become a standard for unresectable HCC. Patients with HCC BCLC class C (advanced stage), or class B who are

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not candidates for TACE, or have progressed after TACE are eligible for systemic therapy. For almost a decade, the treatment of advanced HCC was limited to sorafenib, an anti-angiogenic TKI. Later the first line treatment was updated to a combination of atezolizumab (a programmed death 1 (PD-1) inhibitor) and bevacizumab (an anti-Vascular Endothelial Growth Factor (VEGF)) which was proven to be superior in RCTs (4). Unfortunately, there is still uncertainty regarding the second-line treatments for patients who are still progressing after the first line treatment (5). Two examples of FDA-approved second line treatments are regorafenib (an oral multikinase inhibitor) and nivolumab (a PD-1 inhibitor) (6). Unlike existing reviews, which specifically focus on cases following sorafenib failure, this review takes a broader perspective to gather and compare the available literature regarding the efficacy and safety of these two second-line drugs for patients with unresectable HCC.

Methods

This study was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Literature related to the efficacy of nivolumab treatment in comparison with regorafenib treatment in patients diagnosed with unresectable hepatocellular carcinoma was systematically searched across seven databases, including: PubMed, SCOPUS, Cochrane Database of Systematic Reviews, ScienceDirect, EBSCOhost, EMBASE, and ProQuest. The general search terms used included: "unresectable hepatocellular carcinoma" OR "unresectable HCC", "Nivolumab", "Regorafenib", "Overall survival rate" OR "Progression free survival rate" OR "Adverse event" OR "Safety". The search was performed on April 2nd, 2023, with Table 1 showing the detailed keywords that were used for each database.

There was no limitation of the publishing period, but the language was limited to English. In consideration of the authors' proficiency in English, the decision was made to present this manuscript in English to ensure accurate and effective communication of the content. This choice allows for a comprehensive understanding and coherent presentation of the research findings. Manual searching through references was done to find additional studies. After duplicates were removed, the titles and abstracts were then screened. Potential literature underwent full-text review of suitable papers which were to be included in the data synthesis. Searching and screening were done independently by two investigators and the reasons for exclusion are given in the PRISMA flowchart (Figure 1).

Table 1. Keywords Used for Each Database

Database	Keywords
PubMed	((“Carcinoma, Hepatocellular/therapy”[Mesh]) AND (“Carcinoma, Hepatocellular/surgery”[Mesh])) AND “Nivolumab/therapeutic use”[Mesh] AND “regorafenib”[All Fields] OR regorafenib[Text Word] AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
Scopus	TITLE-ABS-KEY((unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety))
Cochrane Library	((“Carcinoma, Hepatocellular/therapy”[Mesh]) AND (“Carcinoma, Hepatocellular/surgery”[Mesh])) AND “Nivolumab/therapeutic use”[Mesh] AND “regorafenib”[All Fields] OR regorafenib[Text Word] AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
ScienceDirect	(unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
EBSCOhost	(unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
EMBASE	(unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety)
ProQuest	(unresectable hepatocellular carcinoma OR unresectable HCC) AND (nivolumab) AND (regorafenib) AND (overall survival rate OR progression free survival rate OR adverse event OR safety)

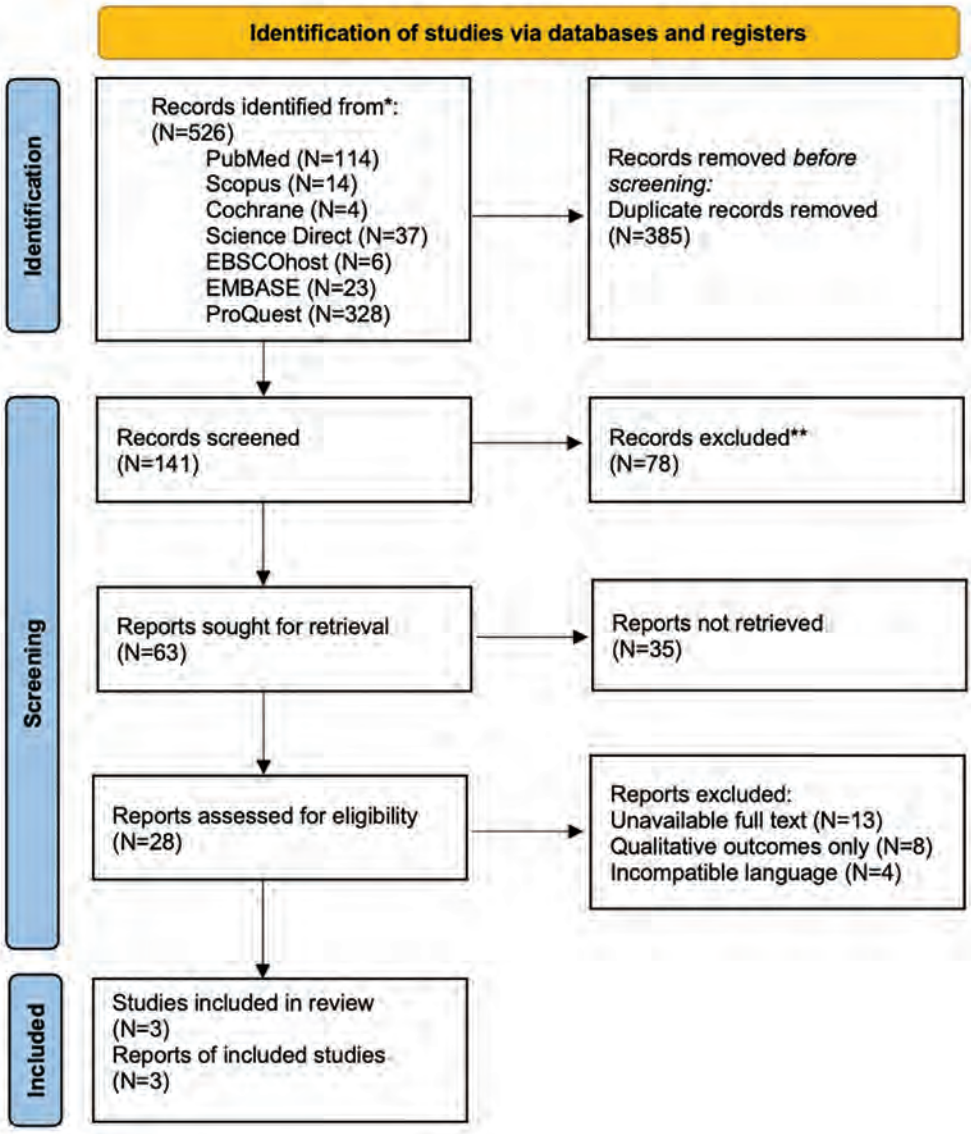

Figure 1. The PRISMA flow diagram of this study.

Study Eligibility Criteria

Inclusion criteria for studies to be included in the analysis were studies: 1) that had subjects diagnosed with unresectable hepatocellular carcinoma; 2) where the subjects were given Nivolumab medication; 3) there was a comparison with the intervention with Regorafenib treatment; and 4) that reported the efficacy of the treatment measured in terms of overall survival, progression-free survival, response rate, and adverse events. The criteria for studies to be excluded were: 1) literature reviews, cross-sectional studies, or case reports; 2) *in vitro* and animal studies; 3) Not using English; 4) Not reporting any quantitative results; 5) Single arm studies or those using a placebo as the comparator. The study designs included were Randomized Controlled Trials (RCT) and cohort studies, due to the high level of evidence in these study designs compared to other intervention study designs.

Data Extraction

The following data were extracted from each eligible study: 1) the authors and year of publication; 2) the study design; 3) the country in which the study was conducted; 4) the inclusion criteria; 5) the number of patients with treatment; 6) the mean age of the study populations; 7) the duration of follow up; 8) study outcomes, which included the parameters overall survival (OS) and/or progression free survival (PFS), time to progression (TTP), tumor response in the form of objective response rate (ORR) and disease control rate (DCR), and safety; 9) summary findings in the study. The data were extracted by two authors independently.

Quality Assessment and Data Synthesis

Quality assessment of the included studies was done using the Agency for Healthcare Research and Quality (AHRQ) tools. Risk of bias was also undertaken comprehensively with the ROBINS-1 tool for non-randomized studies if the studies included were not randomized. A study was considered good if it received 3 or 4 stars in the selection domain AND 1 star in the comparability domain AND 2 or 3 stars in the outcome domain. A study was considered fair if it received 2 stars in the selection domain AND 1 star in the comparability domain AND 2 or 3 stars in the outcome domain. A study was considered poor if it received 0 or 1 star in the selection domain AND 0 stars in the comparability domain AND 0 or 1 star in the outcome domain (7). Extracted data were summarized in tables and narrative synthesis was performed to describe the data. Due to the heterogeneity of the included articles with regard to outcomes of interest to our review, we are unable to analyze and synthesize the data quantitatively. We analysed and reported (qualitative) data in accordance with our study objectives regarding the safety and efficacy of the intervention, which included overall survival, progression-free survival, response rate, and safety in terms of adverse events.

Results

Study Selection

The literature search across seven databases resulted in 526 hits. After removal of 385 duplicates, 141 titles and abstracts were screened to exclude 78 irrelevant papers. Out of the remaining 63 papers, only 28 papers underwent full-text review. There were only three studies that fully met the inclusion criteria, and were hence included in the qualitative data synthesis. The summary of study selection is presented in the PRISMA flow diagram (Figure 1). The list of excluded studies at the full-text level is available in Supplementary File 1.

Study Characteristics and Risk of Bias

All three included studies were retrospective cohort in design, with a total of 383 cohorts who received regorafenib and 230 cohorts who received nivolumab as their second line systemic HCC therapy (8-10). Two of them were from South Korea (conducted in 2020), and one from Taiwan (conducted in 2021). The study by Lee et al. included adult patients with HCC confirmed radiologically or histologically who had received regorafenib or nivolumab. They included 102 patients in the regorafenib group (with a mean age of 62 years old) and 48 patients in the nivolumab groups (with a mean age of 61 years old). Their follow up duration was 1 year and 6 months. The research was supported by the Seoul National University Hospital Research Fund. The study by Choi et al. also included patients with confirmed HCC receiving regorafenib or nivolumab after sorafenib failure, who had Barcelona Clinic Liver Cancer (BCLC) stage B or C, and at least one measurable target lesion based on the modified Response Evaluation Criteria in Solid Tumours (mRECIST). They included 223 patients in the regorafenib group (with a mean age of 58.5 years old) and 150 patients in the nivolumab groups (with a mean age of 56.9 years old). Their follow up duration was six months. The funding was not clearly reported. Lastly, the study by Kuo et al. included patients with unresectable HCC

receiving regorafenib or nivolumab after sorafenib failure, who had Child-Pugh class A or B. They included 58 patients in the regorafenib group (with a mean age of 63.4 years old) and 32 patients in the nivolumab groups (with a mean age of 62 years old). Their follow up duration was one year. Although the funding was not clearly stated, the authors declared that the research was conducted without any commercial or financial relationships that could be taken as a potential conflict of interest. The study characteristics are available in Table 2. Using the AHRQ tools and its standards, all three included studies were assessed to be of good quality. The detailed assessment aspects are available in Table 3. The risk of bias was assessed using ROBINS-I tools, as detailed in Table 4.

Table 2. The Characteristics of Included Studies

Author; year of publication	Study design	Country	Inclusion criteria	Number of patients with treatment		Regorafenib	Nivolumab	Follow up duration
				Regorafenib (dose)	Nivolumab (dose)	Mean age (In years (SD)		
Lee et al., (6) 2020	Retrospective cohort	South Korea	Adult patients (>18 years old), had received regorafenib or nivolumab treatment, confirmed HCC radiologically or histologically.	102 (160 mg once/day for 21 days of each 28 days cycle; adjusted by the amount of 40 mg or transient interruption)	48 (3mg/kg every two weeks)	62 (56-71)	61 (54-67)	1 year and 6 months
Choi et al., (7) 2020	Retrospective cohort	South Korea	Patients that had been diagnosed with HCC based on pathological confirmation and computed imaging, received regorafenib or nivolumab after sorafenib failure, had a BCLC stage B or C, and had at least 1 measurable target lesion based on mRECIST.	223 (160 mg once/day for the first 3 of 4 weeks cycle)	150 (3 mg/kg every two weeks)	N/A	N/A	Minimum of 6 months
Kuo et al., (8) 2021	Retrospective cohort	Taiwan	Patients that had an unresectable HCC (intermediate or advanced stage), received regorafenib or nivolumab after sorafenib failure, and had Child-Pugh class A or B.	58 (160 mg once/day for the first 3 of 4 weeks cycle)	32 (3 mg/kg every two weeks)	N/A	N/A	1 year

SD=Standard Deviation; HCC±Hepatocellular carcinoma; BCLC±Barcelona Clinic Liver Cancer; mRECIST±modified Response Evaluation Criteria in Solid Tumours.

Table 3. Quality Assessment of Included Studies Using the AHRQ Tools

Study	Selection				Comparability	Outcome			Total quality score	AHRQ Standard
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Design or analysis controlled for confounders	Assessment of outcome	Follow-up length	Loss to follow-up rate		
Lee et al., 2020	a (*)	a(*)	a(*)	a(*)	b(*)	b(*)	a(*)	a(*)	8	Good
Choi et al., 2020	a(*)	a(*)	a(*)	a(*)	b(*)	b(*)	a(*)	a(*)	8	Good
Kuo et al., 2021	a(*)	a(*)	a(*)	a(*)	b(*)	b(*)	a(*)	a(*)	8	Good

(*) Stars are given for each of the study aspects.

Table 4. Risk of Bias Assessment of Included Studies Using the ROBINS-I Tools

Study	Pre-intervention			At intervention	Post-intervention				Overall risk of bias
	Representativeness of exposed cohort	Bias due to confounding	Bias in selection of participant into the study	Bias in classification of interven-tions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement outcome	Bias in selection of the reported result	Low/moderate/serious/critical
Lee et al., 2020	low	low	low	low	low	low	low	low	low
Choi et al., 2020	low	low	low	low	low	low	low	low	low
Kuo et al., 2021	low	moderate	low	low	low	low	moderate	low	low

Study Outcomes

All three included studies reported the overall survival, time to progression, tumor response, and safety profile. All three studies showed that HCC patients receiving nivolumab had statistically insignificant longer OS when compared with regorafenib. Lee et al. found statistically significant improvement in OS with nivolumab after multivariate analysis (8). Choi et al. added that there was no significant difference in the PFS (9). Both the studies by Lee et al. and Kuo et al. showed that nivolumab-receiving patients had statistically insignificantly longer TTP than regorafenib-receiving patients (8, 10). In contrast, cohorts receiving regorafenib in the study by Choi et al. showed longer median TTP compared to those receiving nivolumab (although the difference was not statistically significant) (9).

All three studies reported that nivolumab administration in unresectable HCC cases resulted in higher ORR than regorafenib (statistical significance was achieved in two studies). Unfortunately, almost all of them were partial responses and the rate of complete response was very low. Contradicting results were shown in the DCR, as Lee et al. and Kuo et al. both showed that nivolumab resulted in a higher DCR when compared with regorafenib (8, 10). On the other hand, Choi et al. showed that regorafenib resulted in a higher DCR (9). It is important to note that no statistical significance was found in the three included studies. In regards of safety, the superiority of nivolumab over regorafenib was shown in all three studies with lower adverse effect occurrence and better tolerance. The detailed results of the included studies are presented in Table 5, along with the summary findings of each study.

Discussion

The three studies examined overall survival, progression times, tumor responses, and safety profiles in HCC patients treated with nivolumab and regorafenib (Tables 2, 3, and 5). While all the studies showed a trend towards longer overall survival with nivolumab, statistical significance was only found in Lee et al.'s multivariate analysis (8). Time to progression favored nivolumab in two studies, but Choi et al. reported longer times with regorafenib (9). Nivolumab led to higher objective response rates, mainly partial responses, with two studies showing statistical significance. Disease control rates varied across studies, without statistical significance. Overall, nivolumab demonstrated better safety profiles compared to regorafenib in all three studies.

Sorafenib was the only approved systemic treatment of choice for unresectable HCC after the SHARP phase III trial in 2008, which showed a significant, 30% improvement in the OS compared to the placebo group (10.7 vs. 7.9 months) (11). The first line systemic treatment regimen was updated to atezolizumab and bevacizumab after the IMBRACE-150 phase III trial in 2020, which showed 34% improvement in OS and PFS when

Table 5. Outcomes of the Included Studies

Author, year of publication	Study Outcomes				Summary Findings
	Overall Survival and Progression Free Survival	Time to Progression	Tumor Response	Safety	
Lee et al., 2020	Median OS In months (95%CI) Regorafenib: 6.9 (3.5-13.1) Nivolumab: 5.9 (3.2-18.1) P=0.77 by log-rank test Multivariate analysis aHR: 0.54; 95%CI 0.30-0.96 P=0.04 in favor to nivolumab	Median TTP In months (95%CI) Regorafenib: 3.3 (2.0-5.3) Nivolumab: 4.0 (1.8-8.7) P=0.40 by log-rank test Multivariate analysis aHR: 0.81; 95%CI 0.51-1.30 P=0.48 in favour to nivolumab	No patient achieved a complete response Partial response by mRECIST (ORR) Regorafenib: 6/102 (5.9%) Nivolumab: 8/48 (16.7%) P=0.041 in favour to nivolumab DCR Regorafenib: 47.1% Nivolumab: 50.0% P=0.58	Adverse events occurrence Regorafenib: 24/102 (23.5%) Nivolumab: 8/48 (16.7%) P=0.34 Major cause of drug discontinuation: hepatic decompensation (8.3% in nivolumab group and 9.8% in regorafenib group)	Nivolumab was associated with statistically insignificantly longer OS, longer TTP, higher disease control rate, and lower adverse events. Nivolumab showed statistically significantly objective response rate
Choi et al., 2020	Median OS In weeks (95%CI) Regorafenib: 30.9 (28.9-35.6) Nivolumab: 32.6 (21.7-42.9) HR (95%CI) = 0.83 (0.64-1.07) in favour to nivolumab P=0.154 Median PFS In weeks (95%CI) Regorafenib: 12.0 (9.1-13.3) Nivolumab: 7.1 (6.3-10.1) HR (95%CI) = 0.85 (0.69-1.06) in favour to nivolumab P=0.150	Median TTP In weeks (95%CI) Regorafenib: 12.1 (10.6-14.6) Nivolumab: 7.9 (7.0-15.3) HR (95%CI) = 0.95 (0.77-1.19) in favour to nivolumab P=0.680	Only 1/150 (0.7%) of the nivolumab cohort achieved complete response, 19/150 had partial response ORR Regorafenib: 9/223 (4.0%) Nivolumab: 20/150 (13.3%) P=0.002 DCR Regorafenib: 66/223 (48.5%) Nivolumab: 55/150 (40.4%) P=0.222	Rate of dose reductions due to intolerance Regorafenib: 75/223 (33.6%) Nivolumab: 5/150 (3.3%) Rate of toxicity-related discontinuation Regorafenib: 15/223 (6.7%) Nivolumab: 3/150 (2.0%)	Nivolumab was associated with statistically insignificantly longer OS and longer PFS. Although it showed statistically significantly higher ORR and better safety profile
Kuo et al., 2021	Number of deaths Regorafenib: 28 (48.3%) Nivolumab: 17 (53.1%) Median OS In months Regorafenib: 17.3 Nivolumab: 21.9 P=0.966	Median TTP In months Regorafenib: 2.6 Nivolumab: 3 P=0.786	There were 2 (4.3%) had complete response in the regorafenib group ORR Regorafenib: 6.4% Nivolumab: 16% P=0.190 DCR Regorafenib: 31.9% Nivolumab: 44% P=0.309	TRAE Regorafenib: occurred in 68% of patients (the most common is hand-to-food skin reaction in 23.8%) Nivolumab: occurred in 37.5% of patients (the most common is fatigue in 12.1%) P=0.006	Nivolumab had statistically insignificantly longer OS, longer TTP, higher ORR and DCR. It showed statistically significantly lower rate of TRAE.

OS=Overall survival; PFS=Progression free survival; ORR=Objective response rate; DCR=Disease control rate; TRAE=Treatment-related adverse events; CI=Confidence interval; TTP=Time to progression; aHR=Adjusted hazard ratio; mRECIST=modified Response Evaluation Criteria in Solid Tumors.

compared to sorafenib (19.2 vs. 13.4 months) (4). However, there were several other phase III trials conducted, the results of which provided second line treatment options for unresectable HCC. The RESORCE phase III trial in 2017 reported that regorafenib (a multikinase inhibitor) showed a significant, 27% longer OS than the placebo in patients progressing after sorafenib (10.6 vs 7.8 months) (12). Other agents, such as cabozantinib (Celestial phase III trial), ramucirumab (REACH-2 phase III trial), apatinib (ALHEP phase III trial), and pembrolizumab (KEYNOTE-394),

Table 6. AMSTAR-2 Tool for Systematic Review

Domain number	Critical or non-critical	Content of the domain	Yes or partial yes (%)	No (%)
1	Non-critical domain	Did the research questions and inclusion criteria for the review include the components of PICO[a]?	100	0
2	Critical domain	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	0	100
3	Non-critical domain	Did the review authors explain their selection of the study designs for inclusion in the review?	100	0
4	Critical domain	Did the review authors use a comprehensive literature search strategy?	50	50
5	Non-critical domain	Did the review authors perform study selection in duplicate?	100	0
6	Non-critical domain	Did the review authors perform data extraction in duplicate?	100	0
7	Critical domain	Did the review authors provide a list of excluded studies and justify the exclusions?	100	0
8	Non-critical domain	Did the review authors describe the included studies in adequate detail?	100	0
9	Critical domain	Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	100	0
10	Non-critical domain	Did the review authors report on the sources of funding for the studies included in the review?	100	0
11	Critical domain	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	N/A	N/A
12	Non-critical domain	If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?	N/A	N/A
13	Critical domain	Did the review authors account for risk of bias in individual studies when interpreting/ discussing the results of the review?	100	0
14	Non-critical domain	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	N/A	N/A
15	Critical domain	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	N/A	N/A
16	Non-critical domain	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	100	0

also showed superiority in prolonging the overall survival when compared to the placebo (13-16). However, only three regimens (i.e., regorafenib, cabozantinib, and ramucirumab) were approved for the advanced HCC after progression on sorafenib (6).

Three additional second line systemic therapy options were approved on the basis of promising phase Ib/II studies, including nivolumab, pembrolizumab, and ipilimumab (in combination with nivolumab). The CheckMate 040 phase II trial assessed nivolumab as a monotherapy, and demonstrated an ORR of 14% with a median duration of response of 17 months, overall survival was 15.6 months, and the treatment was well tolerated (17). In the CheckMate 459 phase III trial, nivolumab was compared with sorafenib in the first line setting, and a median OS of 16.4 months was reported for nivolumab and 14.7 months for sorafenib (P=0.07) (18).

The improved OS in the nivolumab group compared to the regorafenib group might be explained by the tumor response to the therapy. Targeted therapies, including multikinase inhibitors, have lower response rates and higher therapeutic resistance in HCC as the driver oncogenes have not yet been accurately identified. Hence, most responses are short lived due to the emergence of therapeutic resistance. However, treatment with immune checkpoint inhibitors (such as nivolumab) results in more durable tumor responses, although often in a lower percentage of patients (19). Other studies showed that previous first line systemic treatment might also influence the OS of the second line systemic therapy. Zhai et al. showed that patients receiving regorafenib after receiving lenvatinib showed longer OS compared to those receiving sorafenib as the first line therapy (15.9 vs 11.7 months, P=0.045) (20).

Literature that studied the safety profile of regorafenib in other types of cancer (i.e., metastatic colorectal cancer) also reported similar TEAEs in HCC cases. One study reported that TEAE occurred in 96% of patients, which led to dose reduction in 30% of patients, and treatment discontinuation in 17% of patients (21). Nivolumab monotherapy showed more tolerable adverse effects even when used in other cancer types (i.e., malignant melanoma) with 71% any-grade treatment-related adverse effects and only 10% grade 3 to 4 treatment related adverse events (22). Therefore, the findings in this study are consistent with previous studies regarding the safety and tolerability of the therapy.

The results presented might differ from previous studies due to the differences in patient baseline characteristics. For example, the ORR and DCR observed in the study by Choi et al. were lower when compared with previous phase II trials as previous trials only included patients with Child-Pugh class A and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (9). Therefore, it is important to include the patients' baseline characteristics as well as the treatment regimens (i.e., dosing and duration of treatment) in consideration before interpreting the results of these studies.

Limitations of the Study

This study only includes three studies with a number of cohorts too small to produce a comprehensive comparison between the treatment groups. The three studies included are all retrospective cohorts, as no RCT was found during the literature search. Future studies should include more literature, especially future RCTs, that compare second line systemic treatment options to the first lines or to other second lines. Quantitative analysis should be conducted if adequate literature is available with low heterogeneity, to provide statistical analysis of this comparison. A longer duration of follow up would be ideal to provide more data regarding the OS, TTP, and safety profile of the therapy.

Conclusions

A total of three retrospective cohort studies was found comparing the efficacy and safety of regorafenib and nivolumab as the second-line systemic treatment for unresectable advanced-stage HCC. Nivolumab was shown to generally have longer OS, longer PFS, longer TTP, better ORR, better DCR, and lower adverse events compared to regorafenib. Statistical significance was only achieved in some parameters in each included study. Therefore, the use of nivolumab is preferable as the second line systemic therapy for unresectable HCC. Nevertheless, the patients' baseline characteristics, dosing regimen, and prior therapy should be taken into consideration and may alter the prognosis of the patients. More high-quality studies are urgently needed to generate quantitative analysis and to encourage the formation of guidelines for second line systemic therapy of advanced stage HCC.

What Is Already Known on This Topic:

Atezolizumab (a programmed death 1 (PD-1) inhibitor) and bevacizumab (an anti-Vascular Endothelial Growth Factor (VEGF)) are the first-line treatment of advance and unresectable HCC. For patients who continue to experience disease progression after initial treatment, second line treatment is prescribed. Among the FDA-approved second-line options are regorafenib (an oral multikinase inhibitor) and nivolumab (a PD-1 inhibitor).

What This Study Adds:

In terms of key efficacy and safety outcomes, nivolumab demonstrated superior performance when compared to regorafenib in the treatment of unresectable advanced stage HCC. Nivolumab gave longer overall survival, longer progression free survival, longer time to progression, better objective response rate, better disease control rate, and a lower incidence of adverse events. On the basis of these findings, nivolumab emerges as the preferred choice for second-line systemic therapy in patients with unresectable HCC.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Data Availability Statement: There is no data available.

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Supplementary 1. List of Excluded Studies on the Level of Full Text Assessment

Authors; year	Title	Reasons for exclusion
Grothey et al., 2013	Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial	Unavailable full text
Bruix et al., 2017	Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial	Unavailable full text
Demetri et al., 2013	Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial	Qualitative outcomes
Kim et al., 2023	Regorafenib plus nivolumab in unresectable hepatocellular carcinoma: the phase 2 RENOBATE trial	Unavailable full text
Duffaud et al., 2019	Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study	Unavailable full text
Lei et al., 2022	Efficacy and safety of monotherapy and combination therapy of immune checkpoint inhibitors as first-line treatment for unresectable hepatocellular carcinoma: a systematic review, meta-analysis and network meta-analysis	Unavailable full text
Liu et al., 2021	First-Line Systemic Treatment Strategies for Unresectable Hepatocellular Carcinoma: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials	Unavailable full text
Hsu et al., 2020	Predictors of response and survival in patients with unresectable hepatocellular carcinoma treated with nivolumab: real-world experience	Qualitative outcomes
Jacome et al., 2021	Efficacy and safety associated with immune checkpoint inhibitors in unresectable hepatocellular carcinoma: A meta-analysis	Unavailable full text
Armengol et al., 2018	Hepatocellular carcinoma: Present and future	Incompatible language

Authors; year	Title	Reasons for exclusion
Yoo et al., 2020	Regorafenib in previously treated advanced hepatocellular carcinoma: impact of prior immunotherapy and adverse events	Unavailable full text
Sung et al., 2020	Real-world outcomes of nivolumab in patients with unresectable hepatocellular carcinoma in an endemic area of hepatitis B virus infectio	Qualitative outcomes
Zaniboni et al., 2015	Regorafenib in patients with metastatic colorectal cancer: a review and an update	Incompatible language
Yang et al., 2023	Regorafenib compared to nivolumab after sorafenib failure in patients with hepatocellular carcinoma: A systematic review and meta-analysis	Unavailable full text
Schultheiss et al., 2018	Hepatocellular Carcinoma: New multimodal therapy concepts	Incompatible language
Lee et al., 2022	Determinants of Survival and Post-Progression Outcomes by Sorafenib–Regorafenib Sequencing for Unresectable Hepatocellular Carcinoma	Qualitative outcomes
Vogel et al., 2021	Advances in systemic therapy for the first-line treatment of unresectable HCC	Unavailable full text
Kim et al., 2023	Sorafenib versus nivolumab after lenvatinib treatment failure in patients with advanced hepatocellular carcinoma	Unavailable full text
Kudo et al., 2019	Targeted and immune therapies for hepatocellular carcinoma: predictions for 2019 and beyond	Qualitative outcomes
Parisod et al., 2017	Treatment of advanced hepatocellular carcinoma : Novel agents and role of local therapy	Incompatible language
Fulgenzi et al., 2022	Comparative efficacy of novel combination strategies for unresectable hepatocellular carcinoma: A network metanalysis of phase III trials	Unavailable full text
Xie et al., 2021	Immune checkpoint inhibitor plus tyrosine kinase inhibitor for unresectable hepatocellular carcinoma in the real world	Qualitative outcomes
Hsu et al., 2022	Regorafenib for Taiwanese patients with unresectable hepatocellular carcinoma after sorafenib failure: Impact of alpha-fetoprotein levels	Qualitative outcomes
Personeni et al., 2018	Regorafenib in hepatocellular carcinoma: latest evidence and clinical implications	Qualitative outcomes
Huang et al., 2022	Regorafenib Combined with PD-1 Blockade Immunotherapy versus Regorafenib as Second-Line Treatment for Advanced Hepatocellular Carcinoma: A Multicenter Retrospective Study	Unavailable full text

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Late Adverse Effects after Treatment for Childhood Acute Leukemia

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Abstract
The aim of this review is to raise awareness and knowledge among healthcare professionals and policymakers about late adverse effects in survivors of childhood leukemia. With contemporary treatment, over 90% of children with acute lymphoblastic leukemia (ALL) and over 60% with acute myeloid leukemia (AML) are cured. Large cohort studies demonstrate that 20% of ALL and most AML survivors have at least one chronic health condition by 20-25 years after diagnosis. These are life-changing or threatening in some survivors and contribute to increased premature mortality. We describe the frequency, causes, clinical features, and natural history of the most frequent and severe late adverse effects in childhood leukemia survivors, including subsequent malignant neoplasms, metabolic toxicity, gonadotoxicity and impaired fertility, endocrinopathy and growth disturbances, bone toxicity, central and peripheral neurotoxicity, cardiotoxicity, psychosocial late effects, accelerated ageing and late mortality. The wide range of late effects in survivors of haemopoietic stem cell transplant is highlighted. Recent developments informing the approach to long-term survivorship care are discussed, including electronic personalized patient-specific treatment summaries and care plans such as the Survivor Passport (SurPass), surveillance guidelines and models of care. The importance of ongoing vigilance is stressed given the increasing use of novel targeted drugs with limited experience of long-term outcomes. **Conclusion.** It is vital to raise awareness of the existence and severity of late effects of childhood leukemia therapy among parents, patients, health professionals, and policymakers. Structured long-term surveillance recommendations are necessary to standardize follow-up care.

Key Words: Child ▪ Acute Leukemia ▪ Late Effects ▪ Survivor ▪ Long-Term Follow-Up.

Introduction

The improving cure rate for childhood acute leukemia has been one of the major success stories of contemporary pediatric oncology over recent decades. In high-income countries, over 90% of children with acute lymphoblastic leukemia (ALL), and 60-70% of those with acute myeloid leukemia (AML), are cured. However, this success has been accompanied by considerable long-term toxicity. Large cohort studies demonstrate that 20% of ALL and most AML survivors have at

least one chronic health condition by 20-25 years after diagnosis (1, 2). These "late effects" may be life-changing or threatening and contribute to increased risk of premature mortality.

Many late effects seen in childhood leukemia survivors (CLS) are associated with the same treatments that have played an important role in improving cure rates. It is therefore vital to seek the right balance between increasing treatment intensity (aiming to cure more children) and reducing intensity (to decrease treatment-related late toxicity). Modern treatment regimens seek to use our burgeoning knowledge of leukemia cell and molecular biology to stratify treatment more optimally, reserving more intensive and toxic treatment for those children who need it most whilst avoiding it in those with good prognosis. Pediatric oncologists need a good understanding of the range and nature of late effects to allow them to develop strategies for improving the longevity and quality of survival from leukemia. In addition, it is very important that healthcare professionals (HCP) seeing long-term CLS are aware of the presentations and nature of potential late effects.

This article describes the most common and serious chronic toxicities occurring in CLS. Acute toxicities are not covered except where they lead directly to subsequent late effects. Long-term follow-up (LTFU) and survivorship care are also described.

Epidemiology

CLS represent a growing population, constituting over 30% of all childhood cancer survivors (CCS) (3). Thus, it is increasingly important to characterize the frequency and nature of antileukemic treatment-related late effects. All organ systems are at risk, with late effects including alterations in growth and development, neurocognitive impairment, psychosocial disorders, subsequent malignancies, and cardiovascular, reproductive, musculoskeletal and neurological damage, amongst other toxicities. The overall cumulative burden (expressed as a mean number of events per individual) has been reported as 4.10, 7.96 and 16.71 for childhood ALL survivors, and as 7.24, 11.42 and 18.68 for childhood AML survivors, at 25, 35 and 50 years attained age, respectively (3). CLS experience reduced overall health-related quality of life compared to healthy controls or siblings (4). Whilst many studies have examined long-term morbidity and premature mortality in large cohorts of CCS, few have systematically focused on those treated for childhood leukemia (2, 5, 6). Nevertheless, managing chronic toxicities is essential to provide optimal long-term care once pediatric leukemia has been cured.

Important Late Adverse Effects in Survivors of Childhood Leukemia

Treatment-related, personal and health behavior characteristics that may influence the risk of late effects are depicted in Figure 1. Table 1 lists the nature of and risk factors for late effects as well as recommended clinical evaluation or surveillance tests for at risk survivors.

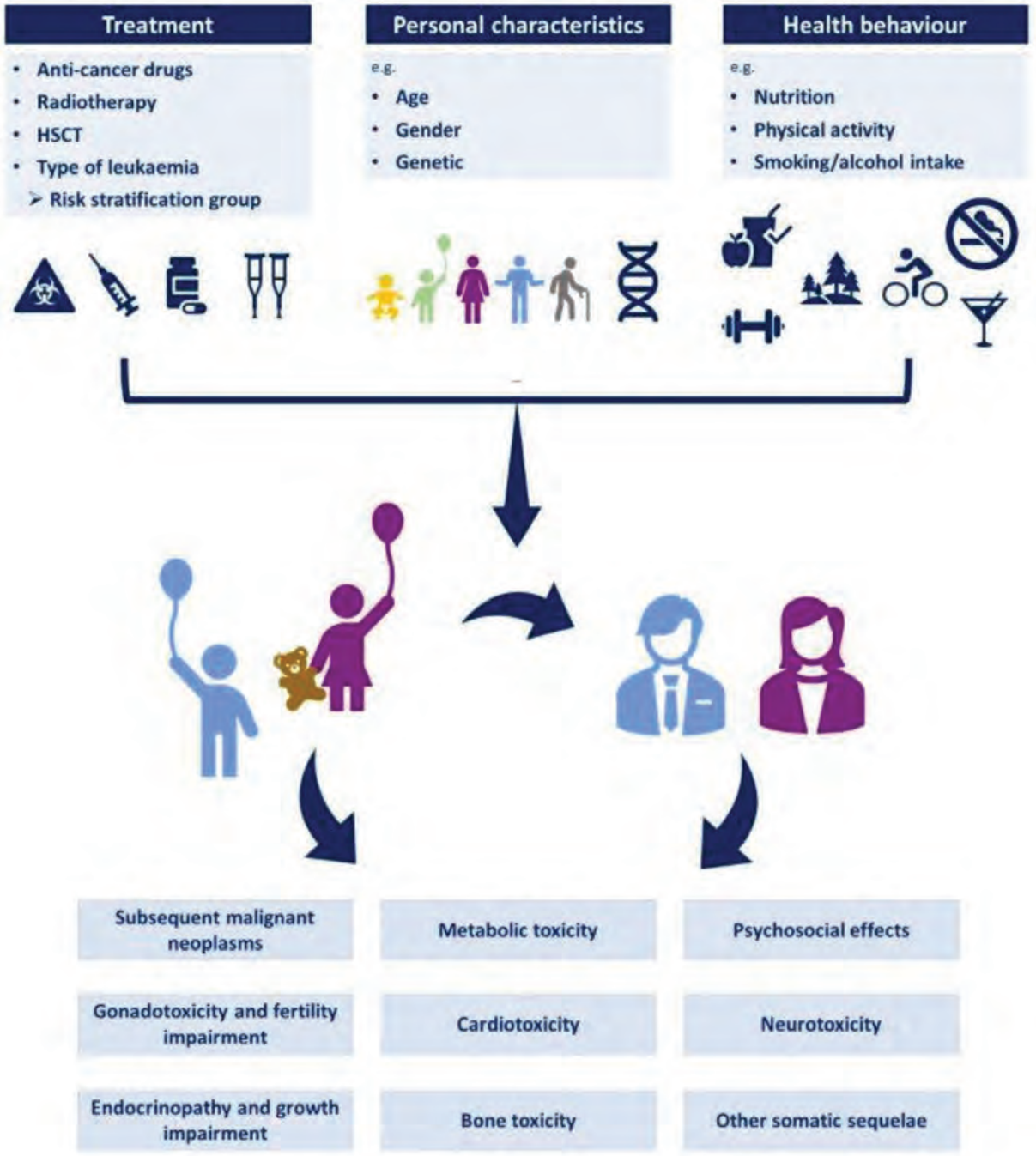

Figure 1. Treatment-related, personal and health behavior characteristics that may influence the risk of late effects in childhood leukemia survivors.

Table 1. Late Adverse Effects, Risk Factors and Recommended Surveillance or Evaluation in Survivors of Childhood Leukaemia*

Late adverse effect	**Patient, disease and treatment-related risk factors**	**Recommended evaluation or surveillance test and frequency** (Recommendations for survivors in absence of surveillance test)
Bone toxicity#		
• Reduced bone mineral density	• Cranial or craniospinal radiotherapy • TBI • Prolonged corticosteroid treatment • Gonadal failure • GHD	• DXA scan at entry into LTFU (2-5 years after completion of treatment), and again at about 25 years age • Additional DXA scans between entry into LTFU and 25 years age, and after 25 years age, may be appropriate as clinically indicated NB: Considered delaying first DXA-scan (until after puberty completed) in pre-pubertal and pubertal survivors
Cardiac toxicity		
• Arrhythmia • Cardiomyopathy • Coronary artery disease (asymptomatic) • Pericardial disease • Valvular heart disease	Arrhythmia	Arrhythmia
	• Anthracyclines[a]	• ECG once at entry into LTFU • Repeat ECG once after the age of 18 years if entry into LTFU was at a younger age
	Cardiomyopathy	Cardiomyopathy
	• Anthracyclines	• Echocardiogram with specific attention to left ventricular systolic function, starting 2 years after treatment • If treated with a total cumulative anthracycline dose ≥250 mg/m^2: at least every 2-3 years • If treated with a cumulative dose ≥100-250 mg/m^2: at least every 5 years • Echocardiogram with specific attention to left ventricular function, prior to pregnancy or in the first trimester, if female and treated with anthracyclines • Screening for modifiable cardiovascular risk factors (hypertension, diabetes, dyslipidaemia, obesity, smoking and low levels of physical activity)
Central nervous system toxicity		
• Cerebral vasculopathy (including cerebrovascular accident [stroke]) • Neurocognitive toxicity (including problems in the cognitive domains of academic and school performance, attention, executive functions, intelligence, language, memory, processing speed or visual-motor integration)	Cerebral vasculopathy	Cerebral vasculopathy
	• Radiotherapy to a volume exposing the head, brain or neck, including TBI	• Discuss importance of controlling cardiovascular and stroke risk factors (hypertension, diabetes, dyslipidaemia, obesity, smoking, low levels of physical activity)
	Neurocognitive toxicity	Neurocognitive toxicity
	• Radiotherapy to a volume exposing the brain, including TBI • High dose IV cytarabine • High dose IV methotrexate • Intrathecal chemotherapy especially if the survivor was treated at a young age	• Medical history with specific attention to educational and/or vocational progress or decline ◆ At least every 2 years in survivors ≤18 years of age ◆ At least every 5 years in survivors >18 years of age Referral to (neuro)psychologist for formal neuropsychological evaluation as clinically indicated
Dental and oral problems		
• Dental caries • Dental developmental problems (especially if treated at a young age or having suffered from poor nutritional condition) • Xerostomia • Periodontal disease	• Radiotherapy to a volume exposing the oral cavity or salivary glands, including TBI • Allogeneic HSCT • Chemotherapy	• Regular dental follow-up

Late adverse effect	**Patient, disease and treatment-related risk factors**	**Recommended evaluation or surveillance test and frequency** (Recommendations for survivors in absence of surveillance test)
Endocrinopathy and growth disturbance		
Endocrinopathy and growth disturbance • HP axis problems (including GHD, TSHD, LH/FSHD and ACTHD) • Precocious puberty (central) (CPP) • Thyroid function problems (including hypothyroidism and hyperthyroidism[b])	HP axis problems; Precocious puberty (central)	HP axis problems
	• Radiotherapy to a volume exposing HP region, including TBI	*Pre-pubertal and peri-pubertal survivors at risk:* • Height velocity in relation to parental height every 6 months • Tanner stage every 6 months • fT_4, TSH, morning cortisol every year • Starting 6-12 months after completion of radiotherapy *Post-pubertal survivors at risk:* • fT_4, TSH, morning cortisol, IGF-1 • Early morning testosterone, or free testosterone in survivors with overweight, and LH (males) • Estradiol, FSH and LH (females) • Every year, starting 6-12 months after completion of radiotherapy • Continue surveillance for at least 15 years from exposure. Continuation of surveillance should be a shared decision between survivor and HCP in the context of the available health care resources. If surveillance is discontinued, the survivor should be educated about possible signs and symptoms of HP axis problems. NB: An IGF-1 level even as high as 0 SDS does not exclude GHD. <u>Precocious puberty (central)</u> *Pre- and peri-pubertal survivors at risk:* • Height velocity in relation to parental height every 6 months • Tanner stage every 6 months • Starting 6-12 months after completion of radiotherapy • Use early morning testosterone (before 10:00 AM) as surveillance modality in pubertal boys who have been exposed to radiotherapy to the testes since testicular volume may be unreliable. • Continue surveillance until the age of 8 years (girls) and 9 years (boys).
	Thyroid function problems	Thyroid function problems
	• Radiotherapy to a volume exposing the thyroid gland, including TBI • Allogeneic HSCT	• TSH and fT_4 measurement • Every year in survivors ≤18 years age and at least every 2-3 years in survivors >18 years age *Female survivors at risk for hypothyroidism:* ◆ Measure TSH and fT_4 prior to attempting pregnancy and periodically during pregnancy
Eye problems		
◆ Cataract ◆ Xerophthalmia ◆ Glaucoma	Cataract	• Medical history with specific attention to symptoms of visual or eye problems • Examination of eye • At least every 5 years
	◆ Radiotherapy to a volume exposing the eye and orbit, including TBI ◆ Prolonged corticosteroids	
	Xerophthalmia	
	◆ Chronic GvHD	
	Glaucoma	
	◆ Prolonged corticosteroids	

Late adverse effect	**Patient, disease and treatment-related risk factors**	**Recommended evaluation or surveillance test and frequency** (Recommendations for survivors in absence of surveillance test)
Fatigue (cancer-related)		
	• All leukemia survivors are at risk for cancer-related fatigue, but the main risk factors are: ◆ Psychological distress ◆ Late effects or health problems ◆ Pain ◆ Older age at follow-up ◆ Radiotherapy	• Medical history focused on survivors' feelings of tiredness and exhaustion • Regularly (at every LTFU visit or general medical check-up)
Gonadotoxicity and fertility impairment		
Gonadotoxicity and fertility impairment • Male - Impaired spermatogenesis - Testosterone deficiency - Physical sexual dysfunction • Female - Premature ovarian insufficiency (including amenorrhea and premature menopause) Fertility impairment as a consequence of any of above manifestations of gonadotoxicity	Male – impaired spermatogenesis	Male – impaired spermatogenesis
	• Alkylating agents • Radiotherapy to a volume exposing the testes, including TBI	*Post-pubertal survivors at risk that desire assessment of potential for future fertility:* • Semen analysis
	Male – testosterone deficiency	Male – testosterone deficiency
	• Radiotherapy ≥12 Gy to a volume exposing the testes, including TBI	*Post-pubertal survivors treated with radiotherapy ≥12 Gy to a volume exposing the testes, including TBI:* • Early morning testosterone at clinically appropriate time intervals • LH in addition to (early morning) testosterone if clinical signs of hypogonadism, previous low or borderline testosterone concentrations, or if an early morning testosterone sample cannot be obtained • At least every 2-3 years
	Male – physical sexual dysfunction	Male – physical sexual dysfunction
	• Testosterone deficiency	• Relevant sexual history
	Female – premature ovarian insufficiency	Female – premature ovarian insufficiency (POI)
	• Alkylating agents • Radiotherapy to a volume exposing the ovaries, including TBI	*Pre- and peri-pubertal survivors at risk:* • FSH and estradiol[c] in case of failure to initiate or progress through puberty at least for girls ≥11 years of age, and for girls with primary amenorrhea (by 16 years of age) *Post-pubertal survivors at risk:* • FSH and estradiol[c,d] in case of menstrual cycle dysfunction suggesting POI, or if assessment of potential for future fertility is desired *Post-pubertal survivors at risk:* • FSH and estradiol[c,d] in case of menstrual cycle dysfunction suggesting POI, or if assessment of potential for future fertility is desired
Iron overload		
	• HSCT • Multiple red blood cell transfusions	• Serum ferritin once at entry into LTFU
Liver toxicity		
	• Radiotherapy to a volume exposing the liver, including TBI • HSCT (irrespective of GvHD) • Methotrexate • Mercaptopurine • Thioguanine • Busulfan • Sinusoidal obstruction syndrome • Chronic GvHD • Chronic viral hepatitis	• Serum liver enzyme concentrations (ALT, AST, gGT, ALP) once at entry into LTFU

Late adverse effect	**Patient, disease and treatment-related risk factors**	**Recommended evaluation or surveillance test and frequency** (Recommendations for survivors in absence of surveillance test)
Lower urinary tract toxicity		
	• Cyclophosphamide • Radiotherapy to a volume exposing the bladder, including TBI	• Medical history with specific attention to urinary tract symptoms • At least every 5 years
Mental health problems		
• Anxiety • Behavioural problems • Depression • Post-traumatic stress • Suicidal ideation	• All leukemia survivors are at risk for mental health problems	• Medical history with focus on survivors' mental health • Regularly (at every LTFU visit or general medical check-up)
Metabolic syndrome and its components		
• Dyslipidemia • Hypertension • Impaired glucose metabolism and diabetes mellitus • Overweight and obesity	Dyslipidemia	Dyslipidemia
	• Cranial radiotherapy • TBI • HSCT	• Fasting lipid profile starting no later than 40 years age, and at least every 5 years subsequently
	Hypertension	Hypertension
	• Radiotherapy to a volume exposing the kidneys, or to a volume exposing the heart and associated large vessels, including TBI • Immunosuppressives, eg cyclosporine, tacrolimus, prolonged corticosteroids	• Blood pressure measurement at least every 2 years and at every LTFU visit
	Impaired glucose metabolism and diabetes mellitus	Impaired glucose metabolism and diabetes mellitus
Psychosocial problems		
• Dependent living • Educational problems • Relationship problems • Social withdrawal • Under-employment or unemployment	• All leukemia survivors are at risk for psychosocial problems	• Social history focused on educational progress and/or vocational planning and employment status and social withdrawal • Regularly (at every LTFU visit or general medical check-up) • At least annually until education is completed
Pulmonary toxicity		
	• Busulfan • Radiotherapy to a volume exposing the lungs, including TBI • Allogeneic HSCT	• Pulmonary function tests, including spirometry and diffusing capacity for carbon monoxide (DLCO), once at entry into LTFU
Renal toxicity		
	• Radiotherapy to a volume exposing the kidney or urinary tract, including TBI • HSCT	*All survivors at risk:* • Glomerular function testing including blood testing (creatinine), urine testing (creatinine, proteinuria), eGFR calculation, at least every 5 years *Other advice:* – Education about caution with the use of NSAIDs
Spleen problems (overwhelming bacterial infections)		
	• Radiotherapy ≥10 Gy to a volume exposing the spleen, including TBI • Allogeneic HSCT (conditioned with or without TBI)	• Patient education about events that necessitate immediate start of therapeutic antibiotics and prompt evaluation by a HCP (ensure antibiotics are readily available) • Advise use of medical bracelet or patient card

Late adverse effect	**Patient, disease and treatment-related risk factors**	**Recommended evaluation or surveillance test and frequency** (Recommendations for survivors in absence of surveillance test)
Subsequent malignant neoplasms		
• Breast cancer (female) • CNS neoplasms (meningiomas, high-grade gliomas and other CNS neoplasms) • Colorectal cancer • Melanoma and non-melanoma skin cancer • Thyroid cancer	Breast cancer (female)	Breast cancer (female)
	• Radiotherapy ≥ 10 Gy to a volume exposing the breasts, including TBI	• Mammography and breast MRI, every year if ≥25 years of age or ≥8 years from radiotherapy, whichever occurs last
	CNS neoplasms	CNS neoplasms
	• Radiotherapy to a volume exposing the head or brain, including TBI	• A decision whether to undertake MRI surveillance should be made by the leukemia survivor and HCP after careful consideration of the potential harms and benefits of surveillance (there is insufficient evidence to make a recommendation for routine MRI surveillance for asymptomatic survivors)
	Colorectal cancer	Colorectal cancer
	• Radiotherapy to a volume exposing the colon and rectum, including TBI	Starting 5 years after radiotherapy or at the age of 30 years, whichever occurs last: • Fecal occult blood testing every 3 years • Alternatively, consider colonoscopy every 5 years
	Melanoma and non-melanoma skin cancer	Melanoma and non-melanoma skin cancer
	• Any radiotherapy, including TBI, predominantly in the radiotherapy field • HSCT, especially with a history of skin GvHD	• Self-examination for new skin lesions and changing moles, at least every 6 months • History at least every 2 years • Skin examination at least every 2 years
	Thyroid cancer	Thyroid cancer
	Radiotherapy to a volume exposing the thyroid gland, including TBI	• Provide counselling regarding options for differentiated thyroid carcinoma surveillance, at least every 5 years • If a decision to commence surveillance is made, make a shared decision for one of these modalities: ◆ Neck palpation, every 1-2 years, starting 5 years after radiotherapy, or ◆ Thyroid ultrasound, every 3-5 years, starting 5 years after radiotherapy

NB

1) This Table lists the more common and / or more serious late adverse effects occurring in childhood leukemia survivors. It is not intended to include all possible late effects.

2) Radiotherapy may be an additional risk factor for some late effects when administered at doses than those usually received by leukemia patients (ie doses than those delivered for cranial or craniospinal radiotherapy, or TBI, in leukemia), but these instances are not included as risk factors in this table due to the lack of evidence of their relevance to leukemia survivors.

Abbreviations: ACTHD = adrenocorticotropic hormone deficiency, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CNS = central nervous system, CPG = clinical practice guideline, DXA = dual-energy X-ray absorptiometry, ECG = electrocardiogram, FSH = follicle stimulating hormone, fT_4 = free thyroxine, gGT = gamma-glutamyltransferase, GHD = growth hormone deficiency, GvHD = graft-versus-host disease, IGF-1 = insulin-like growth factor 1, IV = intravenous, HCP = health care provider, HP = hypothalamic-pituitary, HSCT = hematopoietic stem cell transplantation, LH = luteinising hormone, LH/FSHD = luteinising hormone/follicle stimulating hormone deficiency, LTFU = long-term follow-up, NSAIDs = non-steroidal anti-inflammatory drugs, SDS = standard deviation score, TBI = total body irradiation, TSH = thyroid stimulating hormone, TSHD = thyroid stimulating hormone deficiency.

* Adapted from van Kalsbeek, 2021 (63)

Taken from van Atteveld, 2021 (64)

[a] Anthracyclines include doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone. The following formulas may be used to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Doxorubicin: multiply total dose x 1; Daunorubicin: multiply total dose x 0.6; Epirubicin: multiply total dose x 0.8; Idarubicin: multiply total dose x 5; Mitoxantrone: multiply total dose x 10.

[b] Risk of hypothyroidism for all mentioned exposures. Risk of hyperthyroidism after radiotherapy to a volume exposing the thyroid gland, including TBI, or allogeneic HSCT.

[c] If amenorrhea, measure FSH and estradiol randomly; if oligomenorrhea, measure during early follicular phase (day 2-5)

[d] This assessment should be performed after ending oral contraceptive pill/sex steroid replacement therapy use, if applicable, ideally after two months discontinuation.

Subsequent Malignant Neoplasms

Subsequent malignant neoplasms (SMN) are one of the most serious late effects in long-term survivors of childhood ALL. The reported incidence has varied substantially between 1.8 and 18% in different survivor study populations and treatment eras (5, 7, 8). Compared to survivors treated in the 1970s, those from the 1990s had a lower rate of SMN that was comparable to that of the general population (standardized incidence ratio [SIR] [95% confidence intervals, CI], 1.0 [0.6 to 1.6]), although when stratified by time since leukemia diagnosis the SIR was higher in survivors between 5 and 15 years from diagnosis (SIR 2.3 [1.2-4.0]) (6).

A recent population-based analysis from the United States (US) based Surveillance, Epidemiology, and End Results (SEER-18) database (1973–2014) found that the commonest SMN after pediatric leukemia were thyroid carcinoma (18.3%), sarcoma (15.1%), astrocytoma (10.4%), lymphoma (9.6%), salivary gland carcinoma (7.2%), melanoma (4.4%) and breast cancer (4%) (8). Radiotherapy, chemotherapy and patient-related factors are potential risk factors. Radiotherapy-related SMN mostly occur within the radiotherapy field, and for leukemia survivors, the risk of central nervous system (CNS) tumors including benign or malignant meningiomas and gliomas is increased. Recent evidence suggests that alkylating agent and anthracycline chemotherapy increase the risk of developing certain solid SMN in addition to that of subsequent acute leukemia / myelodysplasia. These risks may be modified by other patient characteristics, such as age at exposure and inherited genetic susceptibility (9). Evidence suggests that the risk of subsequent CNS tumors is reduced in CLS following the elimination of cranial radiotherapy (CRT) for CNS-directed treatment in nearly all children with ALL (2, 5).

The mean duration from ALL diagnosis to development of a SMN has been reported to be about 5 years, and over 76% of SMN in CLS occurred within 20 years of the initial diagnosis However, some SMN (eg breast cancer) may occur 20 years or more after initial diagnosis (8).

SMN have poorer survival rates compared with a first malignancy at the same age, with 5-year survival being 33.1% lower for children (<15-year age at the time of diagnosis of SMN), 20.2% lower for adolescents and young adults (AYA, 15–39-year age), and 8.3% lower for older adults (10). It is uncertain whether this reflects differences in the biological characteristics of SMN compared to equivalent first malignancies, limitations in treatment imposed by therapy already received for the first diagnosis (eg limitations in radiotherapy or chemotherapy dosing due to toxicities) or a combination of these and other factors. This adverse impact on survival highlights the importance of surveillance (see Table 1).

Survivors of childhood AML have been found to have a small increased risk of SMN (SIR 10.6; [3.3-22.3]) and a cumulative incidence of 1.3% at 15 years (11).

Metabolic Syndrome Including Obesity

The metabolic syndrome (MetS) occurs in at least a third of adult survivors of childhood ALL and includes abdominal obesity (defined by increased waist circumference), hypertriglyceridemia, hypercholesterolemia, hypertension and impaired glucose metabolism (12). All these factors increase the risk of developing cardiovascular disease or type II diabetes mellitus (T2DM) leading to increased morbidity and premature mortality. The intrinsic and extrinsic risk factors that contribute the most to the development of these metabolic complications include radiotherapy (specifically CRT and total body irradiation [TBI]), older age at treatment, unhealthy diet, and minimal or no physical activity.

Whilst the prevalence of T2DM in ALL survivors is quite low, the risk in pediatric hematopoietic stem cell transplant (HSCT) survivors is higher and a prevalence of around 9% has been reported (12). Older age at diagnosis and starting puberty during treatment were found to be important risk factors. The influence of asparaginase toxicity with hyperglycemia and/or pancreatitis is not yet fully investigated. Importantly, hyperinsulinemia,

impaired glucose tolerance, hypertriglyceridemia, low concentration of high-density lipoprotein (HDL) cholesterol, and abdominal obesity are more common among HSCT recipients than among non-HSCT leukemia patients.

Obesity, defined as an abnormal or excessive accumulation of body fat, is reported in 11-56% of adult CLS (13). The excess weight gain observed in children treated for ALL usually persists and 40-50% of young adult survivors remain obese (14). Importantly, abdominal obesity is a risk factor for chronic diseases despite normal body mass index (BMI). Risk factors for obesity related to the leukemia treatment are prolonged corticosteroid exposure and CRT leading to hypothalamic damage and potentially growth hormone deficiency (GHD) as well as younger age at diagnosis and female sex. Additional treatment-associated factors include longstanding immobility during treatment, muscle weakness or osteonecrosis (13).

In childhood ALL survivors the standardized mortality hazard ratio is 9.5 (95% CI 8.8–10.2) compared to healthy siblings, with non-cancer related mortality mostly attributed to cardiovascular causes (14). Obesity and other components of the MetS can increase the global risk for cardiovascular complications by 40-fold. Thus, prevention and treatment approaches have become increasingly important to decrease morbidity and mortality (14).

Gonadotoxicity and Fertility Impairment

Fertility impairment has been reported in 42-66% of male and 11-26% of female CCS (15-19) and is higher after alkylating agent treatment and/or radiation to fields involving the testes and ovaries, including TBI (5, 20). ALL survivors treated on older protocols (1962-79) experienced more reproductive system late effects than those treated more recently (1991-2007). Alkylating agents are the most gonadotoxic chemotherapeutic agents and the risk increases with higher cumulative doses, as estimated by the cyclophosphamide equivalent dose (CED) (21). In contrast, methotrexate and vinca alkaloids have minimal or no gonadotoxic effects (22).

Although fertility preservation procedures are seldom feasible at initial diagnosis of acute leukemia due to the child's condition and need for urgent chemotherapy, as well as concerns about leukemic infiltration of gonadal tissue, it remains important that patients and their parents should be counselled about the level of risk of gonadotoxicity. Furthermore, their HCP should ensure timely identification and management of testosterone or estrogen deficiency in at-risk patients and refer survivors to reproductive medicine specialists when appropriate.

Males

Sertoli cells (involved in spermatogenesis) in the testicles are more sensitive to radiotherapy and chemotherapy than Leydig cells (responsible for androgen production).

Chemotherapy agents most often associated with impaired spermatogenesis in male CLS include cyclophosphamide, ifosfamide, busulfan and melphalan (23). Combinations of alkylating agents have an additive effect on gonadotoxicity. Although there is individual variability in the risk of gonadotoxicity after exposure, the cumulative dose likely to produce azoospermia has been established for most agents. Prepubertal status at diagnosis is not protective. Alkylating agent-associated azoospermia is usually permanent although recovery of normal spermatogenesis years after treatment has been described. The testicular germinal epithelium is particularly sensitive to radiotherapy. Testicular doses as low as 0.1 gray (Gy) impair spermatogenesis acutely, and recovery is unlikely after a single testicular dose exceeding 4-6 Gy (23). Testosterone deficiency occurs after testicular radiation of >20 Gy in prepubertal males and after >30 Gy in older boys (23). Subclinical dysfunction of androgen production may occur with lower doses of testicular radiotherapy of 12 Gy (24).

Females

Females are born with a fixed number of ovarian primordial follicles, which varies between individuals and declines with age. Radiotherapy at an older age is associated with greater dose-related risk of ovarian damage, as the result of a smaller oocyte pool at the time of treatment (25). Doses of 5 Gy can impair ovarian function in postpubertal girls (10 Gy in prepubertal), and doses ≥10 Gy (≥15 Gy in prepubertal age) are more likely to cause premature ovarian insufficiency (POI), presenting as amenorrhoea (primary or secondary) or premature menopause (22, 25, 26). Estrogen replacement treatment is required to induce puberty in younger girls with POI and to optimize future cardiac and bone health in post-pubertal individuals. Mathematical modelling of the rate of oocyte decline suggests that the sterilizing dose is 20.3 Gy in infants, 18.4 Gy at age 10 years, and 16.5 Gy at age 20 years. Doses as low as 2 Gy have been estimated to deplete the follicular pool by up to 50% (25). The risk of radiotherapy is increased by additional alkylating chemotherapy. Alkylating agent-induced POI correlates directly with cumulative dose and age at exposure [18]. TBI is a major risk factor for POI. CRT doses causing lower pregnancy rates varied significantly by study, but even low doses (18-24 Gy) used in historical ALL protocols have been reported to decrease fertility rates compared with sibling controls, whilst doses >30 Gy demonstrated the highest risk for fertility impairment due to central hypogonadotropic hypogonadism (22, 26, 27).

Most AML survivors treated with chemotherapy alone had normal pubertal development and fertility. However, anti-Mullerian hormone (AMH) levels were decreased in 13% of post-pubertal females, implying a potential risk of POI in female AML survivors (28).

Endocrinopathy and Growth Disturbances

Endocrine complications are frequently observed in CCS, with 50% of CCS experiencing at least one hormonal disorder during their lifetime (29). The cumulative incidence of grade 1-5 endocrine late effects in CCS is 62.6%, 81.9% and 91.6% at 30, 40 and 50 years attained age, respectively (3). The most common endocrine late effects include hypothalamic-pituitary dysfunction, primary thyroid dysfunction, primary gonadal injury, obesity, T2DM, MetS, and decreased bone mineral density (BMD) (30).

The main risk factors are previous exposure to radiotherapy that included key endocrine organs (hypothalamus/pituitary, thyroid, pancreas and gonads) and/or alkylating agents. The risk increases with the time interval since treatment, the total dose received, fraction size and number, and the method of radiotherapy delivery. In addition to alkylating agents (gonadotoxicity), chemotherapeutic agents associated with endocrine late effects include platinum drugs (gonadotoxicity), glucocorticoids (obesity, decreased BMD), and tyrosine kinase inhibitors (impaired linear growth, primary hypothyroidism) (29).

In childhood ALL survivors the cumulative burden for endocrine late effects was 1.09 at age 30 years and 2.62 at age 50 years, while for childhood AML survivors it was 1.65 at age 30 years and 2.66 at age 50 years (3). All leukemia survivors treated in the 1970s received CRT or (less commonly) craniospinal radiotherapy as part of CNS-directed treatment, mostly with 18-24 Gy. Currently, less than 5% of children with ALL receive CRT. Nevertheless, CRT is a potent cause of hypopituitarism, and the frequency, nature and extent of pituitary hormone deficit is related to dose, the fraction schedule, and the time interval since radiotherapy (30, 31).

The hypothalamus is more radiosensitive than the anterior pituitary gland, so GHD is usually the first endocrinopathy to be diagnosed (32). Survivors who received doses greater than 18 Gy are at highest risk, but even TBI conditioning prior to HSCT with doses of 10 Gy as a single fraction or 12 Gy in 6 fractions may partially reduce growth hormone secretion in 35-50% survivors (30-32). Both younger age and female sex were significantly associated with a greater risk of lower final height in patients treated with CRT (30). Prolactin and thyroid stimulating hormone

(TSH) insufficiencies have also been reported after longer follow-up (30,32,33). It was previously considered that higher radiotherapy doses are needed to cause life-threatening adrenocorticotropic hormone (ACTH) insufficiency, but ACTH insufficiency has been reported in a homogenous group of ALL survivors treated with moderate dose CRT (18-24 Gy) (33). Precocious puberty or rapid progression of puberty can also occur after CRT ≥18 Gy, with female sex and lower age at the time of treatment being additional risk factors (33).

Although the evolution of therapy for childhood ALL has not changed the cumulative burden involving the endocrine system, the specific types of endocrinopathy observed have changed markedly. Endocrinopathies among survivors treated on earlier protocols largely involved adrenal insufficiency and GHD due to chemoradiotherapy-induced hypothalamic-pituitary dysfunction, while impairments in glucose metabolism and body composition and overweight or obesity have become prominent among survivors treated with more recent protocols (5).

Bone Toxicity

Osteonecrosis (avascular necrosis) and low BMD are the two most common bone problems in ALL survivors and may seriously impact quality of life (34). Osteonecrosis is described during and after treatment with high cumulative doses of steroids, HSCT and radiotherapy.

In young adults, BMD is dependent on peak bone mass (PBM). ALL survivors may not have undergone optimal bone growth at puberty due to their illness and treatment (35). Inadequate lean mass acquisition, weight-bearing physical activity, diet, as well as the presence of endocrinopathies, may also impair attainment of PBM (34-36). The prevalence of osteopenia and osteoporosis in CLS is not yet well documented. Moreover, the occurrence of fractures is still insufficiently characterized (37). ALL survivors have the potential highest risk of developing low BMD amongst all CCS as the disease and its specific treatments are the most important risk factors for BMD deficits, namely high cumulative steroid doses, methotrexate, HSCT, CRT and testicular radiotherapy (38).

Low BMD is commonly described during treatment of pediatric ALL, as well as reduced levels of bone formation markers, and this may lead to an increase of fracture incidence (39).

In a study assessing longitudinal BMD and bone structure in ALL survivors who had not received CRT, the findings suggested that ALL treatment in childhood without CRT may not result in long-term detrimental effects on bone development (40). The whole-body bone mass tended to be only marginally lower in long-term allogeneic HSCT survivors than in ALL survivors treated without HSCT, and the size-adjusted bone mass (bone mineral content for bone area) remained normal (41).

Neurotoxicity

Central Nervous System Toxicity

CLS are at risk of long-term neurologic sequelae. One of the most serious consequences is neurocognitive morbidity. Cognitive deficits in CLS treated in the 1970s and 1980s with CRT were frequent, dose-dependent, progressive with duration of follow-up and more pronounced in girls or those treated at a younger age (42). Long-term CLS treated with CRT were found to have significant impairments in memory, task efficiency, and emotional regulation. It was reported that doses of 24 Gy are associated with an average decline in intelligence of about 10 intelligence quotient (IQ) points (43). The most severe delayed neurotoxicity is observed in patients treated with a combination of CRT and neurotoxic systemic and intrathecal chemotherapy. This is probably due to radiation-induced increased permeability of the blood-brain barrier to neurotoxic chemotherapy (44). In more recent decades, leukemia treatment mostly incorporates intensified systemic and intrathecal chemotherapy with methotrexate instead of CRT. Many studies have confirmed that treatment containing chemotherapy alone is still associated with cognitive deficits and other neuropsychologic impairments as well, but to a lesser degree than after

CRT (45). Neurocognitive deficits in ALL survivors include attention, memory, and executive function. These survivors are at higher risk for increased utilization of special education services, poorer academic achievement, higher rates of unemployment, and lower socioeconomic status in adulthood. Adult CLS are at increased risk for late-onset auditory-vestibular-visual sensory deficits, coordination problems, motor problems, seizures and headaches (42). They are also at an increased risk of cerebrovascular vasculopathy, with a relative risk of 6.4 for a cerebrovascular accident (stroke) compared with sibling controls, if treated with CRT (46).

Peripheral Nervous System Toxicity

Clinical manifestations of chemotherapy-induced peripheral neuropathy (CIPN) have been reported in up to 35% of children treated for ALL (47). Vincristine has been identified as the main causative agent. Clinical symptoms include a mixed sensorimotor neuropathy (loss of deep tendon reflexes, paresthesia, neuropathic pain, wrist or foot drop, sensory loss to pain, temperature and proprioception, difficulty with balance and coordination) or autonomic neuropathy (constipation, abdominal pain, paralytic ileus, bladder atony with urinary retention, and orthostatic hypotension). Neurotoxicity can be acute or chronic. Acute neurotoxicity had been thought to be essentially reversible for many years. However, chronic neurotoxicity can occur in a peripheral "stocking and glove" pattern and is an axonal sensory neuropathy that increases with repeated dosing of vincristine. It is often irreversible, with high morbidity and decreased quality of life for many years after treatment completion (48).

Cardiotoxicity

Cardiovascular-related morbidity is a substantial health burden in CCS, and major cardiac events are the leading cause of non-cancer mortality in this population (49). Within 5-10 years after treatment, over 50% of CCS have subclinical evidence of cardiac damage and there is a striking increase in the cumulative incidence of late cardiotoxicity in survivors older than 35 years relative to other health outcomes (49, 50). Late-onset dose-dependent cardiotoxicity is largely due to anthracycline and related agents and chest-directed radiotherapy. Other risk factors include younger age at diagnosis, female gender, longer time since treatment, the presence of pre-existing cardiovascular disease and comorbidities, hyperlipidemia, obesity, diabetes, smoking, and genetic factors (51, 52).

Common cardiovascular adverse events are cardiomyopathy/congestive heart failure, coronary artery disease, stroke, arrhythmias, valvular abnormalities, systemic and pulmonary hypertension, pericardial disease and vascular dysfunction (53). Compared with the general population, CCS were eight times more likely to die from cardiovascular-related disease (54).

CLS had a 4.2-fold increased risk for congestive heart failure, a 3.3-fold increased risk for myocardial infarction, a 2.6-fold increased risk for pericardial disease, and a 2.6-fold increased risk for valvular abnormalities compared with sibling controls (55). In childhood AML survivors, the cumulative incidence of cardiotoxicity was 16% and 27% at 10 and 15 years, respectively (56).

The St Jude Lifetime Cohort Study reported 980 childhood ALL survivors with median time from diagnosis of 30.0 years. The frequency of hypertension was higher among survivors than age- and sex-matched community controls (53.8% versus 43.7%), though not statistically significant, with 18% of survivors having hypertension grade 2 or worse. No difference was found in the frequency of cardiomyopathy or metabolic problems (and modifiable cardiovascular factors) including dyslipidemia, overweight or obesity, and impaired glucose metabolism, between survivors and controls (5).

Psychosocial Late Effects

The experience of leukemia in childhood can have an impact on mental health and social aspects of life long into survivorship. Frequent problems in CCS include depression or anxiety, symptoms

of post-traumatic stress, including intrusion (eg flashbacks), avoidance of situations related to the trauma (eg hospitals), and arousal (eg irritability or concentration difficulties) (57-59). In addition, CCS are at increased risk of suicide ideation as well as completion (57). On the positive side, many CCS, especially after leukemia, also experience positive changes such as post-traumatic growth or benefit finding (57, 59). CCS report an improved experience of relating to others and they find that they also have new possibilities and experience an overall appreciation of life. During the treatment phase, many young leukemia patients miss school for a lengthy period of time and often need educational support thereafter, with survivors of ALL at particular need of further assistance (60). In the long-term, CLS are at higher risk of lower educational achievement compared to their peers (61). In addition, many survivors also experience problems with employment and CLS have a higher risk of unemployment (62).

The high dependency on parents, family and HCP during their diagnosis and treatment generates additional stress when survivors become independent and engage in romantic relationships. Fewer CCS compared to general population are married, and many experience psychosexual problems (61).

Others

Several other late effects such as chronic dental and oral problems, fatigue and pain are well described in CLS. In addition, liver and lower urinary tract toxicity, splenic dysfunction and obstetric problems may occur occasionally in some CLS, most commonly after HSCT. Further information about most frequent and/or more serious late effects, risk factors and recommended evaluation or surveillance test is provided in Table 1 (63, 64).

Accelerated Ageing

There is increasing awareness of the occurrence of accelerated ageing in CCS. In the general population, ageing is characterized by a progressive reduction in physiological reserve capacity clinically manifest as frailty, a syndrome comprising at least three out of the following five markers of low physiological reserve, specifically exhaustion, weakness, low physical activity, slow walking speed and unintentional weight loss. A Childhood Cancer Survivor Study (CCSS) report showed that the prevalence of frailty was three times higher in survivors (6.4% at a mean age of 37.6 years) than in their siblings (2.2% at mean age 42.9 years), and that the risk factors included CRT (65). In addition, a Bone Marrow Transplant Survivor Study (BMTSS) showed that young adult HSCT survivors were more likely than their siblings to be frail at a mean of 8.7 years post-transplant, with those with active chronic graft-versus-host disease (cGvHD) showing a 15-fold increased risk compared to siblings. Furthermore, frail HSCT survivors had a significantly higher risk of subsequent non-relapse mortality over the next 10 years compared to those without frailty (23.9% vs 10.2%) (66). A study in 87 asymptomatic young adult survivors of childhood ALL (median age, 25 years) showed a pattern of chronic inflammation and telomere attrition consistent with early development of the cellular processes driving accelerated ageing (67).

Late Mortality

Late mortality (LM) means death more than five years after diagnosis and reflects premature mortality which may affect CCS. The primary cause of LM is relapse or progression of the first primary cancer even several decades after initial diagnosis, but SMN and cardiovascular causes become the most frequent causes of death later than 20-30 years from diagnosis (68). A large study of children with ALL treated in Europe between 1982 and 2002 found an increased survival over time but also showed that a small excess risk of death persisted for up to 20 years after diagnosis (69). Data from the Italian Off-Therapy Registry found a standardized mortality ratio (SMR) of 11 after ALL and 16 after AML in patients treated between 1960 and 1999 (70). A CCSS study found a reduction in LM after standard-risk ALL comparing the

1970s to the 1990s, with the health-related LM in the 1990s comparable to US population in general. The twenty-year all-cause LM was 6.6 % (6). A separate CCSS study found a SMR of 6.5 for all leukemias treated between 1970 and 1999 (71).

Late Effects after HSCT

Survivors of childhood HSCT have a very high risk of chronic toxicities, with over 90% experiencing at least one and >70% at least three late effects (72). The risk is highest in those conditioned with TBI, but high-dose conditioning chemotherapy also causes considerable late toxicity. Numerous additional and potentially synergistic risk factors contribute to late effects in HSCT survivors, including chemotherapy or radiotherapy given months or years before transplant, sequelae from serious acute complications of HSCT, potentially toxic supportive care drugs, other longer-term complications (eg iron overload due to multiple blood transfusions), and especially cGvHD.

Some post-HSCT late effects, such as SMN, are potentially life-threatening. SMN are reported in up to 10–15% of HSCT survivors 15 years post-transplant, with skin, oral, thyroid and CNS tumors most frequently reported (73). Gonadotoxicity and consequent fertility impairment is frequently life-changing for HSCT survivors (74). Up to 30% of childhood allogeneic HSCT recipients develop cGvHD, with consequent tissue damage that has the potential to affect nearly any body organ or system (75). The range of possible manifestations is very large but commonly involves skin (lichenoid and/or sclerodermatous lesions), musculoskeletal system (sclerodermatous joint contractures), lungs (obstructive lung disease), gastrointestinal tract (oral lesions, gut strictures, malabsorption) and liver (cholestasis). Less commonly cGvHD may affect the kidneys (proteinuria), central (demyelination, vasculitis) and peripheral (myasthenia, neuropathy) nervous systems, and serosal surfaces (pleural, pericardial and peritoneal effusions). In addition, cGvHD may cause immunological impairment (delayed immune reconstitution and risk of late infections) and/or dysregulation (immune-mediated cytopenias), and may contribute to the development of SMN. Serious GvHD (acute or chronic) frequently leads to prolonged and intensive immunosuppressive treatment, contributing to or directly causing long-term toxicities (eg steroid toxicity leading to osteonecrosis and cataracts, renal toxicity due to calcineurin inhibitors). It is important to appreciate that although many of these late effects have multifactorial causes including previous or conditioning chemotherapy or radiotherapy, cGvHD can contribute significantly to adverse long-term outcomes and disability (76).

Survivorship and LTFU

Survivorship Passport

There are between 100-175,000 CLS in Europe, most of whom have already reached or are entering adulthood (77). It is therefore important that at the time of treatment completion or of transition to the LTFU clinic, survivors are provided with a detailed treatment summary containing information on the original leukemia and its treatment (78) as well as recommendations for LTFU ideally based on evidence-based clinical practice guidelines (CPG).

Several initiatives have been developed to provide all CCS with an electronic document containing, in a standardized format, the personal medical history and personalized care plan, both in the US with the Passport for Care (www.passportforcare.org) (79) and in Europe with the Survivorship Passport (SurPass - www.survivorshippassport.org) (80). The SurPass is a web-based tool developed with the support of several European Union (EU) funds and close collaboration amongst late effects experts, pediatric oncologists, survivor organizations and the information technology (IT) company Cineca. The recently released v1.2 of the SurPass combines an individual survivor's health data with International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) / Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare)

evidence-based, international guidelines (63). The main pillars of SurPass are:

Treatment Summary (TS) - Using a common template and internationally approved coding systems, TS is personalized for each survivor. It includes in a standardized format all relevant information about diagnosis, cancer treatment, and any other relevant health data with potential long-term impact on organ function. This will help HCP to quickly understand the survivor's medical history, and survivors themselves to provide access to their own health data.

Survivorship Care Plan (SCP) - Based on the TS and latest IGHG / PanCare CPG (63), algorithms in the SurPass platform generate personalized recommendations for follow-up based on the survivor's risk profile. The SCP can be further tailored by HCP and CCS at each visit by shared decision-making.

The SurPass tool is based on a secure platform and is currently available in eight languages (English, Croatian, Dutch, French, German, Italian, Lithuanian, Spanish) and, if needed, each passport can be automatically translated.

Guidelines

Evidence-based CPG developed with rigorous methodology improve the consistency and quality of clinical care. When widely implemented in general medical practice they have been shown to improve health outcomes and to contribute to reductions in morbidity and mortality. In previous years several CPG for LTFU of CCS have been developed by several European and North American groups, providing surveillance recommendations to facilitate early detection and hence timely intervention to treat or ideally even prevent clinically overt late effects. However, several surveillance recommendations differ between these existing guidelines in terms of identifying groups at risk, as well as in recommended surveillance modalities and timing (81). To overcome these incongruences, IGHG was initiated in 2010 as a worldwide collaboration including researchers from Europe, North America, Australia and Japan to harmonize guidelines for LTFU of childhood and young adult cancer survivors (82). The team includes late effects experts, pediatric and radiation oncologists, other pediatric and medical subspecialists, primary care, nursing, psychology and CCS representatives. So far IGHG has published 15 evidence-based CPG for late effects surveillance (bone mineral density, cancer-related fatigue, cardiomyopathy, coronary artery disease, education / employment outcomes, male gonadotoxicity, hepatic toxicity, hypothalamic/pituitary surveillance, mental health problems, obstetric risks, ototoxicity, POI, subsequent breast and thyroid cancer, and subsequent CNS neoplasms) (82). Each guideline specifies i) who is at risk (needs surveillance) for the given late complication, ii) what surveillance modality should be used, iii), when (at what age or time) should be initiated and discontinued, if applicable, iv) at what frequency should be done, and v) what should be done when abnormalities are found. Further guidelines are under development or planned to be developed by IGHG as well as the update of previous ones in case new evidence from the literature becomes available.

Models of Care

To provide regular and well-organized LTFU for CCS, several models of care have been developed including cancer center-delivered care in a pediatric oncology clinic, medical oncology clinic, or LTFU clinic as the most common model. More recently, follow-up care led by a primary care physician or a shared care model between the treating hospital and the local hospital or primary care have been proposed (83). An important aspect for the choice of care is risk stratification. The risk of CCS suffering late adverse outcomes varies greatly depending on the diagnosis and treatment. CCS at low risk might profit from LTFU by a primary care provider, while those at high risk, such as many CLS, would profit most from attending a specialized LTFU clinic (83). LTFU services perform several important roles including the delivery of ongoing multidisciplinary care, including provision of a TS and SCP with accompanying

education for each CCS, with transition of care from pediatric / adolescent to adult healthcare settings. In addition, late effects surveillance is an important component of care, starting no later than five years after treatment completion or from diagnosis, depending on the individual health care systems, and should be continued life-long, unless specified otherwise.

Future Developments

A great deal of published information is now available regarding the nature, causes and outcomes of late effects in CLS, but several important gaps in knowledge remain. The increasing use of novel immunotherapy and targeted therapies in children with high-risk and relapsed acute leukemia is not only offering these individuals a chance of long-term survival but also revealing their potential to cause a novel range of chronic toxicities many of which are poorly characterized and potentially under-recognized. The ACCELERATE Long-Term Follow-Up Working Group is developing an international LTFU registry to prospectively collect data regarding the chronic toxicities of these treatments (84). Preventive strategies are used increasingly to reduce the risk and severity of some late effects. Greater understanding of the cellular and molecular pathogenesis of late effects may inform the development of new approaches to prevent their occurrence or reduce their severity and may in turn be informed by increased knowledge of the contribution that genetic polymorphisms may play in determining susceptibility to particular toxicities. This information may also ultimately improve risk prediction, informing more accurate late effects counselling for patients and more precisely targeted use of surveillance investigations.

Conclusion

Whilst >90% of children with ALL and >60% with AML are now cured by contemporary treatment strategies, there is increasing recognition of the frequency, nature and potential severity of late adverse effects suffered by long-term survivors, some of which may be life-threatening, life-limiting or life-changing. Despite the rapidly growing body of published literature concerning the wide range of late effects and describing strategies for delivering long-term survivorship care, significant inequalities persist within and between European countries in the availability and quality of such care. It remains of the highest importance to raise awareness of the existence and severity of late effects of childhood leukemia therapy among parents and patients, improve knowledge amongst health professionals, and seek constructive dialogue with policymakers concerning provision and funding of long-term survivorship care.

What Is Already Known on This Topic:

Treatments for childhood acute leukemia have led to substantially improved cure rates, but these lifesaving therapies may also have a long-term impact on survivors' health and quality of life. These late effects include alterations in growth and development, neurocognitive impairment, psychosocial disorders, subsequent malignancies, and organ system damage. All organ systems are at risk, including cardiovascular, endocrine, reproductive, musculoskeletal and neurological, amongst others. The entire landscape of long-term therapy-related complications emerging years or even decades after successful completion of treatment is currently being investigated in collaborative research settings. Many survivors are not aware of their personal risk, and it seems to be a general lack of information among healthcare professionals about potential delayed therapy-related complications. Structured risk-adapted long-term follow-up based on current surveillance guidelines and recommendations offers standardized and optimal health care for childhood leukemia survivors.

What This Study Adds:

Increasing attention is now being focused on issues relating to long-term morbidity and premature mortality associated with the treatments responsible for increased cure rates in the growing population of survivors from childhood acute leukemia. Our knowledge of the late treatment-related adverse events continues to improve through international collaborative research efforts. This review summarizes the most frequent and severe long-term consequences of childhood leukemia therapy. The review describes recent developments in survivorship care approaches, including survivorship passport, surveillance guidelines and models of care, and emphasizes the need for standardized life-long follow-up for childhood leukemia survivors.

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Narrative Review
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Establishment of a Unified Register of Donor Sexual Gametes in the Republic of Kazakhstan

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Abstract

Objective. The purpose of this narrative review paper was to review the state and development of the field of donor gametes in Kazakhstan, compare its legislative and technical capabilities with other countries and identify key steps towards the establishment of a unified register of donor gametes in the Republic. **Materials and Methods.** The narrative review paper conducted an analysis of scientific publications and legal documents to examine the implementation of Assisted Reproductive Technologies (ART), focusing on Donor Sexual Gametes (DSG), globally. It utilized medical publications from 2019 to 2023, legal acts, and recommendations from global health organizations to analyze eligibility criteria, legal regulations, and the social aspects of ART across different regions. **Results.** In Kazakhstan, ART is regulated by legislation, with DSG procedures governed by age limits, medical screening, and restrictions on the number of children born from donated gametes. Worldwide, practices vary, but there is growing interest in establishing a unified register of reproductive donor material to enhance transparency and accountability. However, legal gaps and ethical considerations must be addressed. **Conclusion.** The study identifies gaps in Kazakhstan's legislation compared to Western countries, emphasizing the necessity for enhanced legal rights for donors and recipients, including options for anonymity. Ethical concerns highlight the importance of confidentiality and data security in accessing the donor registry. Overall, implementing such a register promises to enhance transparency, safety, and accountability in reproductive medicine.

Key Words: Assisted Reproductive Technologies ▪ In Vitro Fertilisation ▪ Reproductology ▪ Infertility ▪ Fertilisation.

Introduction

The most common causes of infertility in medical practice are tubal-peritoneal pathologies, endocrine disorders, organic lesions of the reproductive system, and male factor infertility (1). Regardless of the aetiology of infertility in each case, a country's healthcare system should establish the most effective legal and technical conditions for assisted and curative therapy for patients. One of the key areas of medical and public health development in the last decades in the world is reproductive medicine, namely the issue of the donation of sexual gametes (DSG) and the development of legislative and material basis for its implementation (2, 3). Reproductive medicine is intended to solve problems with conception and carrying a pregnancy in patients where in vitro fertilisation (IVF) methods are the only possible method for successful conception (4, 5). Donor-to-recipient DSG is one of these techniques.

The latest reproductive medicine technologies have already been incorporated into infertility treatment protocols, which underlines the significance of developing companion bases and registries for the successful use of DSG. In the Republic of Kazakhstan, the problems of preserving and supporting motherhood and childhood, and ensuring

the reproductive health of citizens, are always emphasised, both by presidential programmes and by the Ministry of Health (6). Despite the active introduction of new reproductive developments in the field of assisted reproductive technologies (ART), statistical indicators of infertility prevalence remain stable. Globally, more than 15% of couples of reproductive age experience infertility each year (7).

Due to the availability of genetic and molecular diagnostic methods, the number of diagnoses leading to infertility remains high (8, 9). With the development of reproductology in Kazakhstan, there is an increased need for the development of both treatment and counselling centres within the health care system (10) and modern registers of DSG for the legislative activity of such institutions (11).

The purpose of this narrative review paper was to analyse the scientific data on the experience of the legal regulation of ART, in particular donation of sexual cells (DSC) in the Republic of Kazakhstan and countries in Europe and the United States, to establish basic principles for the development of a unified register of donor cells in Kazakhstan, as part of the implementation of modern ART methods.

Materials and Methods

This section gives an analysis of the scientific data on assisted reproductive technology (ART), particularly gamete donation, in the Republic of Kazakhstan and other countries worldwide. A comprehensive search of scientific publications in obstetrics, gynaecology, reproductology, laboratory diagnostics, embryology, internal medicine, and social medicine was conducted using reputable databases, such as: Ebsco, Google Scholar, ResearchGate, PubMed, Medscape, and Clarivate. Only publications from 2019 to 2023 from high-impact factor journals and evidence-based global scientific publications were included.

The search strategy employed advanced and evidence-based data, reflecting results from long-term studies and observations in practical medicine. Comparative legal analysis was conducted by examining legal acts, including constitutions, codes, ministry of health orders, United Nations conventions, and protocols from organizations such as the American Society for Reproductive Medicine. The inclusion criteria for research data were strict, focusing on medical publications from relevant and reputable sources. The analysis also incorporated the latest recommendations from the World Health Organization and international associations related to ART regulation. Additionally, social aspects of gamete donation were explored using data from large-scale social surveys of donors and recipients.

The review compared legal regulations of ART across different countries, examining factors such as: eligibility requirements, donor and recipient rights, age criteria, compensation options, and anonymity policies. Both the legal and social dimensions of gamete donation were scrutinized to provide a comprehensive understanding of its practice and implementation globally.

Moreover, the review assessed the integration of international recommendations into the practice of reproductive and epidemiological institutions in Kazakhstan, encompassing both state-run and private facilities. By synthesizing data from various sources, this review aims to contribute to the current understanding of ART regulation and practice, with implications for policy development and clinical management in Kazakhstan and beyond.

Results

Legislative Framework and Terminology of ART in the Republic of Kazakhstan

The Constitution of the Republic of Kazakhstan presents one of the basic rights of citizens in Article 27: the right to establish a family and continuation of birth: “marriage and family, maternity, paternity, and childhood are under the protection of the state.” The right to receive reproductive medical services is inherent and a constitutive right of citizens of the Republic governed by international regulations, specifically the United Nations

Convention on "the elimination of all forms of discrimination against women" (18.12.1979), to which the Republic of Kazakhstan is a party. In Kazakhstan, reproductive medicine programmes, in particular ART, are implemented with the active participation of legislation (11). It ensures that medical workers in the field of reproductive medicine and obstetrics follow clear rules when working with the subjects of ART, and excludes unfair conduct of ART programmes or using gametes, organs, and tissues beyond their intended use.

ART is a set of medical interventions aimed at treating infertility, in which the fusion of male and female gametes and the subsequent stages of embryonic development occur outside the female body (12). The first laboratory facility for IVF in the Republic of Kazakhstan was established in 1995; in 1996, the first child was born using ART (10). In 2020, the Code on Public Health and the Health Care System was updated in the Republic of Kazakhstan, which defines the basic principles for conducting ART programmes in the population. The principles regarding the organisation of ART are outlined in Article 148 of the Code, separate from other types of ART. In addition to the Code, the Republic of Kazakhstan has Orders No. KR DSM 236/2020 ("On Approval of the Rules and Conditions for the Conduct of DSC, and Tissues of Reproductive Organs") and 272/2020 ("On Approval of the Rules and Conditions for the Conduct of ART"), which outline the rules and legitimacy of DSC in the country. The current Code of the Republic of Kazakhstan defines other options for ART, including artificial insemination and IVF. The DSC procedure is defined at the legislative level of the Republic (6, 10) as a method of overcoming diagnosed infertility when used in the scope of treatment. In vitro fertilisation is included in several guaranteed-free services in the health care system within the framework of state programmes for a cohort of patients with direct medical indications for its performance as part of infertility treatment.

The subjects who can legitimately use ART methods in the Republic of Kazakhstan, especially DSG, include married couples (a man or a woman with a diagnosis of infertility) or single people who are not married but have indications for a reproductive procedure. For the subjects of ART who are not officially married, it is necessary to provide written consent for the medical manipulation. The general regulation of legislative relations during the implementation of ART is delegated to the Ministry of Health of the Republic of Kazakhstan (10). In addition to written consent and the requirements listed in the Code, there is also an Order of the Minister of Health of Kazakhstan No. KR DSM 272/2020 that lists extra requirements for ART. These include medical indications that have been diagnosed (as listed above), being of reproductive age, and not having any immediate reasons why the manipulation should not be done.

DSG is considered within the legal framework as one of the ART options used to treat infertility but is frequently interpreted as a technique outside the list of ARTs. According to the Code, DSG can be applied to subjects in the age range of 18–35 years who have proof of full somatic and psychological health and have undergone genetic screening. The limit of 35 years of age for DSG appears in other Ministry Orders, meaning that it always remains lower than for participants in ART. In addition, such subjects must sign consent to implement the rules outlined in the protocol of the DSC. The quantitative range for the possible continuation of participation in the DSC for donors is prescribed: the birth of ten children from one donor during the DSG is a criterion for the exclusion of the subject from the ART programmes and using the gametes of this respondent for recipients. In addition, the donor does not receive information about the use and trajectory of sexual gametes as part of the commitment to implement the ART procedure.

DSG has some limitations in its application to date. On the one hand, it is associated with possible risks of accidental biological relatedness between offspring due to using material from the same donor for several recipients (8). It provides a space for the establishment of both a unified registry of reproductive material on a national scale and possibly a unified registry of donors (eggs and

sperm), which could operate on the scale of countries with a legally regulated process for the implementation of ART and DSC (13). In addition, medical tourism, where the export of reproductive material is realised in other countries, is a necessity.

Worldwide Practices in the Implementation of DSG

The legal position and accessibility of ART in Kazakhstan have some unresolved and unspecified issues in the sphere of medical provision of reproductive services and the sphere of the reproductive rights of donors and recipients during the implementation of DSG. The idea of establishing a unified register of ARTs today faces many enormous problems (14): from the collection of factual information on the institutions, health workers, and actors involved in the implementation of ARTs in the country, to the development of a legal framework for the establishment of an official state register to regular monitoring of donor material and the results of its (successful or unsuccessful) use. For example, embryo donation is prohibited in multiple countries, including Austria and Iceland (Table 1).

Examining the global landscape of ART implementation highlights diverse approaches across countries. While some nations, like Kazakhstan and the United States, offer both paid and free options for donation, others, like France and Spain, provide donation services free of charge. Variations also exist in quantitative restrictions for donors, with limits on the number of children born from donated gametes ranging from 3 to 10 across different countries. Mandatory medical screening before donation procedures ensures the safety and health of both donors and recipients, with age restrictions typically falling within the range of 18 to 35 years.

Table 1. Features of Implementation of the Donation of Sexual Gametes (oocytes and Sperms) in Different Countries of the World

Country	Donation of sexual gametes			
	Options for conducting	Quantitative restrictions for donors	Medical screening before donation procedure	Donor age range (Years)
Republic of Kazakhstan	Paid and free	Up to 10 children born	Obligatory	18-35*
United States of America	Paid and free	Up to 6 children born	Obligatory	18-35†. 18-43‡
France	Free	Up to 6 children born	Obligatory	18-35*
Spain	Paid and free§	Up to 6 children born	Obligatory	18-35*
Norway	Paid and free	Up to 6 children born	Obligatory	18-35*
Switzerland	Paid	Up to 8 children born	Obligatory	18-35*
United Kingdom	Paid and free	Up to 10 children born	Obligatory	18-35*
Denmark	Paid and free	Up to 6 children born	Obligatory	18-45*
Canada	Paid and free	Up to 8 children born	Obligatory	18-35*
Australia	Paid and free	Up to 5 children born	Obligatory	18-35*
Japan	Free	Up to 6 children born	Obligatory	18-49*
China	Free	Up to 3 children born	Obligatory	20-45†, 20-40‡
New Zealand	Paid and free	Up to 10 children born	Obligatory	18-45*
Brazil	Free	Up to 6 children born	Obligatory	18-35*
Argentina	Free	Up to 6 children born	Obligatory	18-35*

Source: Compiled by the authors; *Years for donors and recipients; †For donors; ‡For recipients; §Donor compensation is possible.

Despite all challenges, the idea of establishing a unified register of reproductive donor material is gaining traction, especially in light of rapid advancements in reproductive technologies and the increasing prevalence of medical tourism in pursuit of ART services. However, it is essential to address legal gaps and ethical concerns to ensure the responsible and ethical implementation of such a register globally.

In conclusion, while the implementation of ART varies significantly across countries, the concept of a unified register holds promise for enhancing transparency, safety, and accountability in the field of reproductive medicine. Efforts to address legal and ethical challenges are crucial in realizing the potential benefits of such a registry and ensuring equitable access to ART services worldwide. Considering the rapid progress in the development of reproductive technologies and medical tourism to receive ART, which frequently outpaces changes in legislation and the ethical dogmas of countries (15), the idea of establishing a unified register of reproductive donor material becomes more realistic and feasible (16, 17).

Features of Creating a Unified Register of DSGs in the Republic of Kazakhstan

When establishing a unified register of donor gametes, it is essential to consider the fact that the current legal documents of Kazakhstan do not include the recipient's right to possess information on the results of the donor's medical examination (general clinical, psychiatric, and genetic), nationality, or race. In addition, cyto- and molecular-genetic diagnostic methods are not included in the list of compulsory tests before participation in ART. Research conducted in private and public reproductive centres (8) on more than 1500 patients demonstrates that the risks of diagnosing chromosomal variability in couples with infertility and aggravated obstetric histories are significantly higher than in patients with normal reproductive functions. There is a need for legislative approval of compulsory cytogenetic and molecular genetic tests for patients with reproductive disorders before using DSG.

The establishment of a unified register of sexual gametes provides for clear control over the use of and implementation of sexual gametes in reproductive institutions. It establishes the foundation for obtaining objective information in court proceedings. The donor does not have the right to appeal against revelation of their biological parenthood in cases of genetic confirmation of paternity (18). An equally significant issue is the religious bias of the ethnic group (19) where DSG is performed. Whereas in some countries donors and recipients have more liberal opinions on the possibility of germ cell donation (single patients, patients with non-traditional orientation) (20), in others such possibilities will only be implemented for married couples. This is an essential aspect that should be considered both in the selection of participants in the DSG and for the designation of donation material in the registry.

Discussion

Kazakhstan has an emerging legislative framework to regulate assisted reproductive technologies such as gamete donation programmes, but there are still gaps compared to more established systems in European countries and the United States. Our results highlight the lack of mandatory genetic testing for donors and recipients, limited rights for recipients to access medical information on donors, the narrow age range for access compared to some countries, and no centralised registry to track the use and outcomes of donated materials.

The analysis highlighted the need to expand legal rights for both donors and recipients during the donation process. Similar to evolving standards in Western countries (21), participants should have clear options in relation to maintaining anonymity and access to medical records. Religious and ethnic considerations must also be carefully weighed (19). Ultimately, the legal framework in Kazakhstan must strive for an appropriate balance between safety, transparency, accessibility, and confidentiality—one that accounts for unique

social norms while upholding international standards.

The ethical issue of access to the register of donors and recipients of sexual gametes (DSG) raises important considerations regarding privacy, confidentiality, and accountability (22). While recipients may have a vested interest in accessing the register for various reasons, including concerns about genetic health and familial history, granting direct access to individuals may compromise the confidentiality and anonymity of donors (23, 24). Social research on egg donors in Kazakhstan has highlighted the importance of maintaining donor confidentiality, with a significant percentage expressing a desire for complete anonymity. In the opinion of the authors of the current research, access to the register should be limited to authorized healthcare professionals and the national authorities responsible for oversight and regulation. Allowing recipients or donors direct access to the register could potentially breach confidentiality and compromise the anonymity of donors, which may deter individuals from participating in donation programs. Moreover, the establishment of a unified register should prioritize the protection of donor privacy and confidentiality, while still providing recipients with essential information about the use of reproductive material (25).

To address concerns about confidentiality and data security, it is crucial to implement robust safeguards and protocols to protect the integrity of the register. Informative meetings should be conducted regarding the safety of electronic technologies and the legal rights of donors to retain personal data, to ensure transparency and informed decision-making. Additionally, donor information agreements should explicitly address potential risks, such as technical vulnerabilities and data loss, and outline measures to mitigate these risks (26). Thus, while access to the register of donors and recipients of sexual gametes can provide valuable information for recipients and healthcare professionals, it is essential to prioritize the confidentiality and privacy of donors. Limiting access to authorized personnel and implementing stringent security measures can help maintain the integrity of the register while protecting the rights and anonymity of donors (27, 28).

These findings align with other recent research indicating that the rights of ART participants in Kazakhstan are not as robust as in many Western countries. A 2022 study found that only 43% of egg donors in Kazakhstan were satisfied with the information they received on the accounting and outcomes of their donations (16). This is far lower than rates of upwards of 80% seen in the United Kingdom and Spain (29-31). Our analysis also supports calls for expanded genetic testing, given research showing high risks of chromosomal variations in Kazakh couples struggling with infertility (8).

The Spanish Fertility Association published data according to which almost four out of every ten children in Spain were born through ART in 2020 and were dependent on the DSG procedure. In the Republic of Kazakhstan, as indicated above, these figures are lower. A healthcare provider in Spain has the option of choosing the recipient's reproductive material while taking the donor's phenotypic traits into account (32). Our results provide a strong rationale for establishing a unified gamete registry in Kazakhstan, modelled after registries in the United States, Spain, and regional programmes in Europe (14). Centralised tracking of donor materials is the norm globally, and provides critical oversight while protecting confidentiality through encryption and access controls. As Kazakhstan continues to advance ART services, implementing such a registry will ensure best practices.

In some countries, the anonymous donation of germ cells is mandatory, in order to control the confidentiality of participants in ART (e.g., Spain). However, in other countries around the world, non-anonymous donation of gametes with open information about the recipient and the donor is the only option for participation in ART (Sweden, Norway). In a third option, as in several other countries, the status of the openness of personal data rests on the decisions of the donor or recipient themselves when registering for the procedure (e.g., USA and Iceland). Access to ART is only available to heterosexual married couples in countries

such as Lithuania, Albania, the Czech Republic, Italy, Poland, Slovakia, and Switzerland, although in most countries ART is available to single people or homosexual couples (e.g. in France) (33).

Cryopreservation of germ cells for diseases affecting fertility is permitted in most countries with ART, frequently despite restrictions in specific legislation (12). In addition to the preservation of gametes, the preservation of sex glands and embryos for medical reasons is practiced in European countries (33). During the legal regulation of ART, most countries offer financial assistance to families suffering from infertility and to donors of sexual gametes (34). State legislation should consider the main financial cost drivers of ART: drug prices, labour costs for health workers, and laboratory services. In Europe, public funding programmes for ART may cover donors and recipients for all three components of the procedure or for one of the components (medicines, health care providers in private or public reproductive centres, or laboratory screening). However, in Albania, Georgia, and Switzerland, there is no state financial coverage for ART.

Regulation of access to the register of donors and recipients, the balance between the legal protection of donors' personal information and the maximum medical awareness of reproductive material for the recipient, and the technical reliability of information digital data storage and processing—these and many additional issues are to be regulated during the development of a unified database of donor sexual gametes in the Republic of Kazakhstan.

Conclusion

The legislative framework in Kazakhstan, while comprehensive, exhibits gaps compared to more established systems in Europe and the United States. Key findings include the lack of mandatory genetic testing for donors and recipients, limited rights for recipients to access medical information on donors, and the absence of a centralized registry to track usage and outcomes of donated materials.

There is a need for expanded legal rights for both donors and recipients, clear options regarding maintaining anonymity, and careful consideration of religious and ethnic norms. Ethical concerns regarding access to the register of donors and recipients emphasize the importance of confidentiality, accountability, and data security. While recipients may have legitimate reasons for accessing the register, limiting access to authorized healthcare professionals and national authorities is essential to protect donor anonymity and confidentiality.

The study underscores the urgent need to address legal gaps and ethical concerns to ensure the responsible and ethical implementation of a unified register of reproductive donor material. Efforts to enhance transparency, safety and accountability in the field of reproductive medicine are crucial, considering the rapid advancements in reproductive technologies and the increasing prevalence of medical tourism. Overall, the establishment of a unified register holds promise for improving ART practices, but careful attention to legal, ethical, and technical considerations is paramount to its success.

What Is Already Known on This Topic:
In Kazakhstan, egg and sperm donation is regulated by the Code and several regulations, which outline the age range of participants, the list of tests for donor screening, and indications for the procedures. There is a need to establish a unified register of gamete donors to regulate using the material, control the number of children born from donors, and maintain the confidentiality of participants.

What This Study Adds:
This study provides a comparative analysis of the legal regulation of gamete donation in different countries, offering a theoretical basis for the development of a strategy for establishing a unified register of donors in Kazakhstan. It shows how important it is for lawmakers to agree that people with reproductive disorders who want to use sexual gamete donations must first go through cytogenetic and molecular genetic tests.

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Case Report with Review of Literature
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Spontaneous Bleeding in Vestibular Schwannoma in Patients on Oral Anticoagulant Therapy: Report of Two Cases and Review of Literature

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Abstract

Objective. Anticoagulant therapy is a risk factor for repeated intratumoral hemorrhage and acute enlargement of a vestibular schwannoma (VS) with neurological deficits. Therefore, we describe two cases of patients on oral anticoagulant therapy with intratumoral hemorrhage in which anticoagulant therapy prior to surgical resection was discontinued. We also discuss other similar cases from the literature since this is a rare event. **Case Reports.** We described the two cases of intratumoral hemorrhage in acoustic neurinoma and conducted a literature review of similar cases of patients with intratumoral hemorrhage in acoustic neurinoma who were also on oral anticoagulants. Both patients presented with CN-VII palsy prior to surgery; both also fully recovered after surgery except for hearing loss on the tumor side. Our literature review found 50 cases of VS (reported as vestibular schwannomas in the literature) with intratumoral hemorrhage. From this total, 11 patients used oral anticoagulant therapy with reported poor outcomes and high mortality; 9 of these 11 cases were reported in the past 20 years. The incidence is expected to rise due to increased use of anticoagulant therapy due to onset of atrial fibrillation, atherosclerosis, and thromboembolism from longer human lifespan. **Conclusion.** Anticoagulant therapy represents a risk factor for intratumoral hemorrhage and acute enlargement of VS tumor mass with neurological deficits.

Key Words: Anticoagulants ▪ Hemorrhage ▪ Neuroma ▪ Acoustic ▪ Risk Factors ▪ Vestibular Schwannoma.

Introduction

Vestibular schwannomas (VS), represent 80% of cerebellopontine angle (CPA) tumors and roughly 8% of all intracranial neoplasms (1). These types of tumors commonly present with slow and progressive hearing loss, tinnitus, disequilibrium, and vertigo (1). Intratumoral hemorrhage (ITH) is a potentially devastating development associated with VSs due to the close proximity of the brainstem, the confined anatomy of the posterior fossa, and the potential for acute fourth ventricular obstruction. Patients may deteriorate rapidly, and in some instances the tumor can become sizable and potentially life-threatening (2-5). Common risk factors for ITH in VS are anticoagulant therapy (6), and previous radiation therapy (7, 8), as well as hypertension (9), trauma (10), pregnancy (11), tumor size >25 mm (5, 12, 13), and high tumor vascularization (14). Surgical treatment is the therapy of choice in patients with VS who present with ITH (5, 15). The use of antithrombotic agents, either antiplatelet or anticoagulant drugs has increased due to longer human lifespan and increased incidence of atrial fibrillation, atherosclerosis, and thromboembolism (16).

Herein, we present two cases of patients with oral anticoagulant therapy who presented with acute onset of facial nerve (CN-VII) palsy and symptoms

of raised intracranial pressure due to ITH and enlargement of the tumor size with brain stem compression. The senior author (KIA) operated on both patients.

Case Presentations

Case 1

A 56-year-old male with headache and acute onset of left CN-VII palsy with a House-Brackmann (HB) score of Grade III (i.e., moderate nerve damage) presented to our clinic. The patient experienced progressive left-sided hearing loss several years prior to acute onset of CN-VII palsy. The patient was on anticoagulant therapy with warfarin due to atrial fibrillation. Post-contrast magnetic resonance imaging (MRI) of the head revealed a left-sided VS with intratumoral bleeding (Figure 1). The patient underwent surgical treatment 3 days after initial presentation. Urgent surgery was not performed due to the need to optimize the coagulation status of the patient first, and also due to the fact that the patient did not neurologically deteriorate. Warfarin therapy was paused and therapy with low-molecular-weight heparin (LMWH) was applied due to indication for persistent anticoagulation due to atrial fibrillation. Preoperative substitution of the coagulation factors with prothrombin complex concentrate (PCC) until normalization of the international normalized ratio (INR) was applied. Gross total resection of the VS was performed via suboccipital retrosigmoid approach. Intratumoral bleeding was demonstrated in the course of surgical resection. The patient recovered his facial nerve palsy and was neurologically intact apart from complete hearing loss on the left side (Figure 2). Postoperative MRI revealed resection of the tumor (Figure 3). Warfarin therapy was continued 4 weeks following surgery, which overlapped with LMWH.

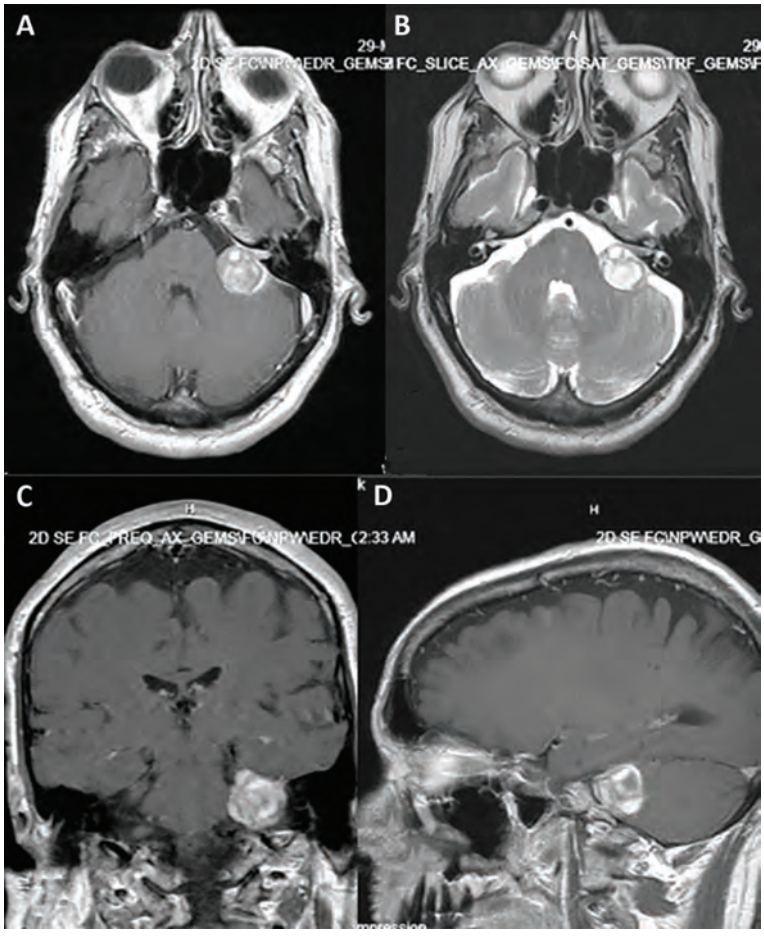

Figure 1. Preoperative head MRI of a 56-year-old patient with acute onset of left CN-VII palsy. **(A)** Axial T1-post contrast MRI, **(B)** axial T2 MRI, **(C)** coronal T1-post contrast, and **(D)** sagittal T1-post contrast head MRI shows left sided VS with signs of intratumoral bleeding and effacement of the pons.

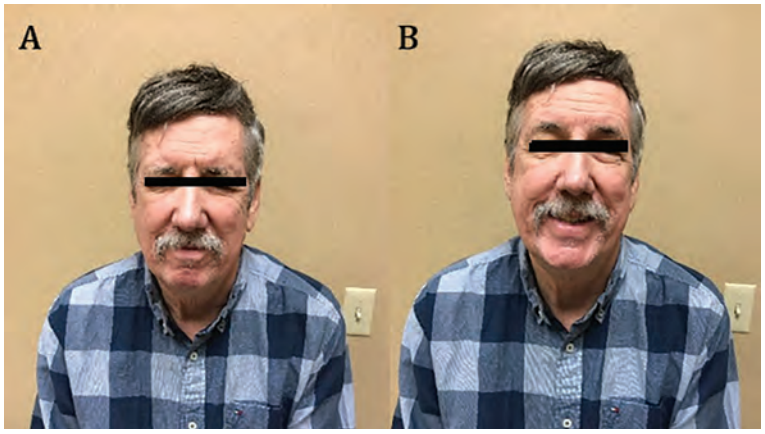

Figure 2. Patient from Figure 1 at 3 months follow up. CN-VII palsy resolved completely.

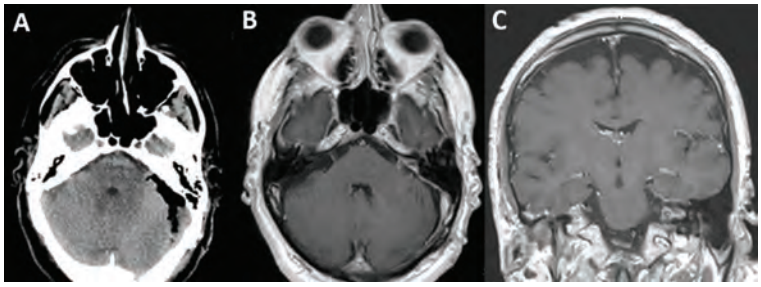

Figure 3. Postoperative imaging of the patient. **(A)** immediate postoperative CT of the head following surgery. **(B)** Axial and **(C)** coronal postoperative post-contrast head MRI showing resection of the tumor.

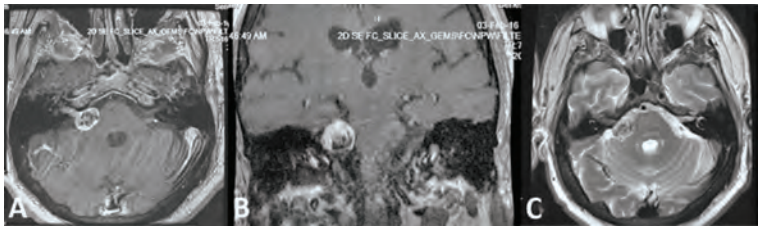

Figure 4. Initial T1-weighted post-contrast MRI of the 58-year-old patient (Case 2). **(A)** Axial, **(B)** coronal, and **(C)** T2 axial views show right-sided VS. The tumor was followed up.

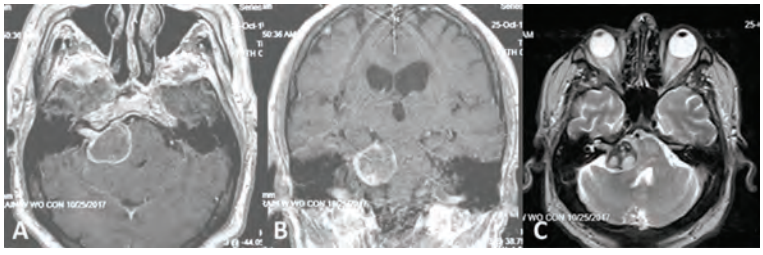

Figure 5. MRI of the patient from Case 2 on warfarin therapy due to artificial heart valve, showing enlarged VS on the left side with intratumoral bleeding. **(A)** T1 weighted axial MRI, **(B)** T1 weighted coronal post-contrast MRI of the head, and **(C)** axial T2 weighted MRI of the head show intratumoral hemorrhage.

Case 2

A 58-year-old male with known right-sided VS diagnosed due to progressive right-sided hearing loss (Figure 4). The tumor was followed up due to patient refusal for surgical or radiosurgical treatment. The patient was morbidly obese with a known history of heart failure with an ejection fraction (EF) of 20%, an artificial heart valve, and treatment with warfarin therapy. The patient presented 3 years prior after initial MRI with headache, acute onset of CN-VII palsy on the right side, complete hemifacial numbness, and inability to walk. Subsequent MRI revealed an enlarged right sided VS with ITH and compression of the brain stem (Figure 5). Warfarin therapy was paused and LMWH was applied due to the indication for persistent anticoagulation related to the patient's artificial heart valve. Preoperative substitution of the coagulation factors with prothrombocyte concentrate until normalization of the international normalized ratio (INR) was applied. Surgery was performed 3 days following the initial presentation with a subtotal resection of the VS via the suboccipital retrosigmoid approach. Intratumoral bleeding was demonstrated during the resection, but the patient significantly improved his facial nerve palsy and was neurologically intact apart from complete hearing loss on the left side (Figure 6). Postoperative MRI revealed subtotal resection of the tumor (Figure 7). Warfarin was continued 4 weeks following surgery, which overlapped with LMWH.

Figure 6. Patient from Figures 4 and 5 at 3-month follow-up with significant improvement of the CN-VII palsy (from Gr V to Gr III).

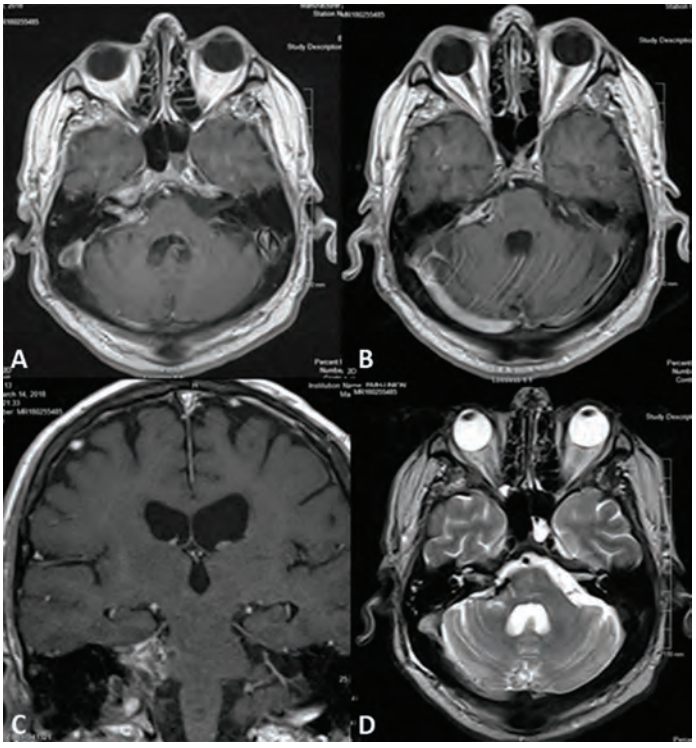

Figure 7. Postoperative head MRI at 3-month follow up shows subtotal resection of the tumor. **(A)** Post-contrast MRI of the head axial T1-weighted image in the level of the internal meatus and **(B)** axial T1-weigted image in the level of apex of the pyramid, and **(C)** coronal T1-weighted and **(D)** axial T2-weighted MRIs show subtotal resection of the tumor without brain stem compression (45).

Discussion

ITH in VS is a rare but well-known event. Most commonly, it happens in cystic cases and not in solid cases. It is estimated that tumor-associated hemorrhage in VS occurs in 0.4% of cases and commonly presents with acute neurological change (6). However, prospective analyses have suggested that ITH might be a part of the natural history of VS (5). Microbleeding in the tumor bed of VSs with subsequent fibrosis is a described phenomenon, which has been proposed as a possible mechanism for hearing loss in these tumors (17). On the molecular level, it has been postulated that ITH, vessel density, and the inflammatory reaction contribute to volume increase of sporadic VSs (18). Cystic and inhomogeneous tumors showed significantly more hemosiderin deposition than homogeneous tumors, and micro-vessel density was significantly higher in tumors with a high number of CD68-positive cells (18). Intratumoral microhemorrhage is a possible mechanism of pathogenesis in cystic VS, characterized by unpredictable expansion of the cyst component (1). Most VSs demonstrate microhemorrhages on T2-weighted gradient-echo (GRE) MRI, which is useful for differentiating these tumors from meningiomas of the CPA (17).

Clinically significant ITH occurs in approximately 11% of all brain tumors and is most common in glioblastoma multiforme, choriocarcinomas, pituitary adenomas, meningiomas, choroid plexus papillomas, and oligodendrogliomas (9). Intratumor bleeding in an VS can lead to a rapid and profound onset of symptoms due to the limited confines of the posterior fossa and the immediate expansion of tumor size, which results in severe headaches, nausea and vomiting, abrupt deterioration in hearing, and a significantly higher

incidence of facial weakness (15). Mathkour et al. found 48 cases of intratumoral hemorrhage in patients with VSs in 30 published articles in the period 1974–2019 (15). One further review of 39 cases with ITH in VS showed an average tumor size of 3.11±1.12 cm; the authors postulated that patient age and tumor size in hemorrhagic cases of VS did not differ significantly from non-hemorrhagic cases of VS (5). Carlson et al., in a retrospective case series, found that anticoagulated patients had a 25-fold increase in significant VS hemorrhage (6). Facial nerve dysfunction at presentation occurred with greater frequency in cases of hemorrhagic VS (33.3%) than in non-hemorrhagic VS (6.0%), and death occurred more frequently in cases of hemorrhagic VS (10.0%) than in non-hemorrhagic VS (0.2%) (5). Abnormality of tumor-associated vasculature was noted histologically in many cases, and many the cases reported prior treatment by stereotactic radiosurgery (5). Cystic formation, large size, mixed Antoni type, and anticoagulation therapy seem to enhance the risk of tumor hemorrhage (19). Risk of ITH in patients with VS has been shown to be related to hypertension (9), trauma (10), pregnancy (11), tumor size >25 mm (5, 12, 13), high tumor vascularization (14), cocaine use (20), methotrexate (21), and weight lifting (22). The prognosis of surgery for patients with acute hemorrhagic VS may be better than that for microhemorrhage in multicystic VS (9). Timely microsurgical treatment is also important to relieve symptoms (9).

Antithrombotic agent use has increased as human longevity leads to increased atrial fibrillation, atherosclerosis, and thromboembolism (16). Six million Americans have been found to use anticoagulant drugs (~2% of the population), putting them at an increased risk of ITH (23). A recent meta-analyses revealed that anticoagulation therapy in patients with brain tumors due to venous thromboembolism was not associated with an increased risk of intracerebral hemorrhage (ICH) in the setting of brain metastasis; however, anticoagulation therapy use resulted in a greater than 3-fold increased risk of ICH in patients with gliomas (24, 25). Direct oral anticoagulants (DOACs) have brought advantages in the management of many patients, with evidence showing a lower risk of intracranial bleeding versus vitamin K antagonists (VKAs) (26). However, due to the increased number of anticoagulated patients worldwide, major and life threatening oral anticoagulant-related bleeding is also increasing, and effective reversal strategies are needed (26).

The risk of clinically significant hemorrhage increases 25-fold in patients receiving anticoagulation versus the general VS population (6, 27). Anticoagulation treatment, as well as previous radiation therapy, appear to be crucial risk factors for subarachnoid hemorrhage from an VS (7), as well as for ITH (8). Interestingly, recent literature emphasized the use of anticoagulant therapy as a major risk factor for ITH in VS but did not analyze this issue further (5, 15). This issue was not addressed specifically in Mathktour et al. (15). Niknafs et al. described only 2 cases of anticoagulant therapy with ITH in VS (5). Out of 78 patients reported with bleeding in acoustic neurinomas reported until 2022, there were 9 cases that used anticoagulation therapy (11.5%) (28).

The first case report on intratumoral bleeding in patient with VS on oral anticoagulant therapy was published in 1987 (29). A 58-year-old man bled into an undiagnosed VS while on long-term anticoagulation therapy, which was started following aortic valve replacement. The patient presented with multiple cranial nerve-paralysis of sudden onset. The tumor was removed sub-totally, but the patient died 5 days postoperatively from recurrent hemorrhage into the tumor bed (29). Duration of anticoagulation is not necessarily a strong predictor of hemorrhage risk with VS (6). Prior to the year 2000, there was one additional case report of ITH in VS in a patient taking aspirin (30). We identified 9 cases in 8 articles with ITH in VS due to use of oral anticoagulant therapy in the past 20 years (Table 1).

Table 1. Literature Review on ITH in Patients on Oral Anticoagulant Therapy with VS

Author and year	Cases (age, gender)	Oral anticoagulant therapy	Comorbidities	Side and size	Previous diagnosis and treatment of the VS	Presentation	Hydrocephalus	Reversal of coagulation therapy	Surgical treatment	Outcome
Vellin et al., 2006 (33)	73, F	Anti Vitamin-K overdose (INR not specified)	Arterial hypertension		No	Rapid onset of headache, facial palsy, diplopia, and hoarseness	Yes	Not specified	No	Massive intratumoral and brainstem bleeding, coma and death 3 days following admission
Yates et al., 2010 (34)	69, M	Warfarin (INR not specified)	Hypertension, hyperlipidemia, coronary artery disease with myocardial infarction, paroxysmal atrial fibrillation.	Left, 3.2x2.6 cm	No	CN-VII palsy (HB IV), decreased facial sensation on the left, wheel-chair-bound due to disequilibrium, no other focal neurologic signs; patient was alert and oriented; moderate-to-severe sensorineural hearing loss on the left with poor word recognition ability	Yes	Warfarin dosing was discontinued; patient was given interim therapy with LMWH to continue anticoagulation until surgery	Scheduled for urgent, non-emergent surgery	Emergent ventricular drain due to hydrocephalus and re-bleeding 2 days following admission; posterior fossa craniectomy and evacuation of hematoma for decompression; death on the first post-operative day
Carlson et al., 2017 (6)	Case 1: 39, M	Warfarin (INR, 2.8)	Atrial septal defect, hypertrophic nonobstructive cardiomyopathy, severe pulmonary hypertension	Left, 4.2 cm^3	No	HA, Diz, HL, ataxia, hemiparesis	Yes	Not specified	GTR via retrosigmoid approach; VP shunt due to hydrocephalus	CN-VII (HB VI) (complete resolution), improvement of ataxia and disequilibrium
	Case 3: 68, M	Long term low dose aspirin followed by warfarin and enoxaparin 2 weeks prior to ITH due to pulmonary embolism (INR, 2.3)	Hypertension, diabetes, pulmonary embolism	Right, 3.1 cm^3	No	Headache, dizziness, hearing loss, CN-VII paresis (HB IV), hypoesthesia	Yes	Not specified	STR via retrosigmoid approach, VP shunt due to hydrocephalus	CN-VII palsy (HB I) (CN-VII was not preserved during surgery)
Schlieter et al., 2005 (32)	49, M	Phenprocoumon (INR, >7)	Not specified	Right, 15 mm axial diameter	No	Acute right-side palsy of the CN-VII and CN-VIII, acute hearing loss, headache, vertigo, and vomiting.	No	Not specified	Surgical resection, details not specified	7th cranial nerve dysfunction improved slightly, deafness

Continuation of Table 1.

Author and year	Cases (age, gender)	Oral anticoagulant therapy	Comorbidities	Side and size	Previous diagnosis and treatment of the VS	Presentation	Hydrocephalus	Reversal of coagulation therapy	Surgical treatment	Outcome
Ganslandt et al., 2008 (19)	72, F	Warfarin (INR not specified)	Cardiac arrhythmia	Left, initially 3.8 cm^3	Yes VP Shunt due to hydrocephalus and SRS with 35 Gy	15 months after SRS sudden onset of hemiparesis and progressive loss of consciousness due to ITH, additional bleeding into the cerebellum and compression of the brain stem.	Yes	Not specified	Emergent resection via posterior fossa decompression	Death following surgery due to central regulation failure
Moscovici et al., 2020 (7)	67, F	Warfarin (INR, 5.5)	Mechanical aortic valve replacement for which patient was taking warfarin, obstructive sleep apnea, hypertension, depression, morbid obesity, type 2 diabetes	Left, 12x20.5 mm with subarachnoid hemorrhage	Yes SRS with 12 Gy in a single fraction 7 years before acute onset	Sudden onset of disequilibrium, HA, vomiting, diplopia and left sided facial weakness, hyperlacrimation and intermittent hemifacial spasm, CN VII palsy (HB IV) as well as abducens palsy	No	Prothrombinex and Vitamin K	Semi-urgent elective GTR via translabyrinthine approach	The degree of left facial nerve palsy appeared to be similar (HB IV); however, symptoms of disequilibrium improved
Banaama et al., 2016 (12)	76, F	Anticoagulant therapy (not specified)	Hypertension, hypercholesterolemia, thrombosis of the right carotid artery, acute myocardial infarction, total knee replacement, thoracic and lumbar fractures, diabetic retinopathy, aortic valve replacement, coronary artery bypass surgery, postoperative arterial fibrillation	Left, giant, size not specified	Yes Diagnosis of polycystic VS due to hearing loss 5 years prior to initial presentation	Severe headache and a facial palsy House and HB V	Yes	Not specified	Emergent surgery for hematoma evacuation and partial resection of the VS via retrosigmoid approach	Death due to rebleeding 36 hours following initial surgery

Continuation of Table 1.

Author and year	Cases (age, gender)	Oral anticoagulant therapy	Comorbidities	Side and size	Previous diagnosis and treatment of the VS	Presentation	Hydrocephalus	Reversal of coagulation therapy	Surgical treatment	Outcome
Rizk et al., 2019 (45)	83, M	Antiplatelet drug (aspirin and clopidogrel)	Coronary heart disease, stents	Left, cystic, size not specified	Yes Diagnosis of left sided VS 2.5 years prior to surgery due to CN-VII palsy (HB V) and hearing loss	Follow up MRI without new symptoms showed approximately 3 times enlargement of the tumor with ITH	No	After holding aspirin and clopidogrel for 5 days, surgery was performed within 3 weeks of the onset of facial weakness	STR through retrosigmoid approach	Neurologically unchanged with persistent CN-VII palsy (HB V)

GTR=Gross total resection; HB=House-Brackmann; INR=International normalized ratio; ITH=Intratumoral hemorrhage; LMWH=Low-molecular-weight heparin; MRI=Magnetic resonance imaging; SRS=Stereotactic radiosurgery; STR=Sub-total resection; VP=Ventriculoperitoneal; VS=Vestibularschwannoma.

Because the risk of hemorrhage in VS is significantly greater with systemic anticoagulation, and because reports have demonstrated poorer clinical outcomes while on anticoagulation therapy, the management of this subset of patients becomes a critical point of discussion (6). One fifth of all reported cases of ITH in VS were using oral anticoagulant therapy. Seven fatalities have been reported so far in patients with ITH in VS (15); out of these, 4 were patients on oral anticoagulant therapy. In the setting of significant ITH, cranial nerve-VII dysfunction is observed in 46.9% of cases (6); in contrast, all patients on oral anticoagulant therapy had a sudden onset or worsening of CN-VII palsy. A recent review of 47 cases of hemorrhagic VS showed that 7 patients experienced improved facial nerve function after resection, with the remainder either remaining unchanged or not reported (15). In comparison, our 2 cases have excellent outcome with complete resolution of symptoms and CN-VII palsy. Out of 9 reported cases, VS was previously diagnosed in 4 patients; in 2 cases, observation with follow up MRI scans was performed; in 2 further cases, stereotactic radiosurgery (SRS) was performed. One patient who was followed up and one patient who underwent SRS died following urgent surgery for ITH in VS. ITH after VS radiosurgery is a rare phenomenon with a cumulative incidence rate of 0.26% (31). Given the poor outcome with high mortality and improvement of CN-VII palsy only in 2 out of 5 patients who survived ITH in VS, we recommend surgical treatment at initial diagnosis for patients on oral anticoagulant therapy in order to prevent secondary ITH and acute enlargement of the tumor mass. The most common oral anticoagulants were overdosed vitamin-K-antagonist warfarin (Coumadin, Jantoven) and phenprocoumon. Fortunately, reversal of anticoagulant effect is very easily possible with PCC. Out of 6 patients on warfarin, warfarin was overdosed in 4 cases (Table 1)—2 cases from Carlson et al. (6), and 1 case each from Schlieter et al. (32) and Moscovici et al. (7). Velin et al. (33), Yates et al. (34) and Ganslandt et al. (19) did not specify INR.

As for aspirin use, there is currently a Phase II study on use of aspirin as a possible medication therapy to halt progression of vestibular schwannomas (35). In a previous retrospective study of 347 vestibular schwannoma patients seen at Mass Eye and Ear, the probability of a tumor growth in patients who took aspirin for unrelated medical reasons was about half that of patients who did not take aspirin. However, that trend was not observed in retrospective studies from other institutions (36).

It seems that anticoagulation treatment acts as a secondary trigger to intratumoral microhemorrhages by enhancing bleeding and preventing the self-tamponade phenomenon achieved by the tumor's capsule (6). In hemorrhagic VS, 1 out of 5

patients were previously treated with SRS (5). A 7-element bundle for treating major or life-threatening oral anticoagulant-associated bleeding has been proposed and includes the following: (a) withdrawing the anticoagulant until local hemostasis is safe; (b) replacing fluids; (c) conducting blood tests (hemoglobin level, platelet count, renal function, liver function, prothrombin time [PT], and activated prothrombin time [aPTT]), and DOAC plasma level when necessary; (d) transfusing red blood cells, platelets and/or fresh frozen plasma, and tranexamic acid; (e) measuring local hemostasis (endoscopy, interventional radiology procedure or surgical intervention); (f) checking and managing additional bleeding risk factor; and (g) reversing the anticoagulant effect (26). Specific reversal is possible for direct thrombin inhibitors (idarucizumab for dabigatran) and factor Xa inhibitors (andexanet for apixaban, edoxaban, and rivaroxaban); in addition, non-specific reversal treatment can be used for both of these medication groups as well as for vitamin K antagonists PCC (37), which was the strategy used in our two cases. Guidelines suggest that patients with major or life-threatening vitamin K antagonist-associated bleeding should be promptly treated with 4-factor PCCs at doses tailored on INR value in addition to intravenous vitamin K (38). A histological review of 274 VS specimens revealed that nearly all exhibited varying levels of intratumoral microhemorrhage, and more extensively involved tumors were independently associated with preoperative unserviceable hearing (39). It has also been suggested that multiple hemorrhagic events could account for the existence of cystic VS that comprise 5%–10% of tumors and are widely described as demonstrating rapid growth, shorter symptom durations, and worse outcomes after resection (40). In a histopathologic examination of VS, Niknafs et al. reported 2 vascular abnormalities, including dilated thin-walled vessels and hypervascularity in every specimen examined. These vascular abnormalities likely predispose the tumor to develop microhemorrhages (5). Recently, matrix metalloproteinase II activity within the tumor, which leads to vascular fragility and microhemorrhage, has been proposed as a causative agent in VS cystic degeneration (41).

Several recommendations regarding the use of anticoagulation in VS patients have been proposed, such as tight management of INR to avoid supratherapeutic levels that may increase the risk and severity of hemorrhage, reevaluation of the need for anticoagulation and finding alternatives to systemic anticoagulation (such as cardioversion or ablation for arrhythmia when feasible), and maintaining a low threshold for intracranial imaging following any change in neurological symptoms (done under the assumption that earlier recognition can result in improved outcome) (6). Most patients on long-term anticoagulation with small-to-medium sized VSs are treated conservatively with observation or radiotherapy due to the risks associated with surgery (6). Based on a limited clinical data, Carlson et al. suggested that observation is the best initial treatment strategy for anticoagulated patients with small or medium sized tumor (6). DOACs were not associated with an increased incidence of ICH relative to LMWH in patients with brain metastases or primary brain tumors (42).

As a possible alternative to surgical treatment, Shelfer et al. proposed a discontinuation of the oral anticoagulant therapy in a case report of an elderly female patient with VS and a high risk of falls without previous history of strokes (43). The authors thought that since the patient was a high fall risk, the potential consequences of a head injury with intracranial bleeding on anticoagulation therapy outweighed the risk of atrial fibrillation–related embolus formation (43). A study of 48 patients between 70 to 90 years of age with VS recommended that surgical resection is a good option in patients >70 years of age with a tumor size <1.5 cm if the patient's hearing is viable, the tumor demonstrates a growth of more than 2 mm per year, and the patient is in good general health. If one of these 3 criteria is not met, then follow up was recommended with serial imaging (30, 44). Yates et al. recommended consideration of anticoagulant therapy when deciding between surgery and conservative management (34). The risk of hemorrhage with

antiplatelet therapy was not evaluated so far but is relevant to VS since recent data suggested that cyclooxygenase inhibitors, such as aspirin, may reduce the probability of future tumor growth in conservatively managed VS (36).

Both our cases were solid in nature. Surgery was performed with gross total resection in one case and subtotal resection in the second case. The CN-VII palsy resolved fully and there were no further neurological deficits apart from deafness on the side of the lesion. We also conducted a literature review of patients on oral anticoagulant therapy who underwent surgical treatment due to ITH in VS, which shows that oral anticoagulant therapy increases the risk of ITH in VS, as well as poor outcomes that prompt surgical treatment. To our knowledge this is the first article on two cases of patients on oral anticoagulant therapy with ITH in VS with a literature review solely dedicated to ITH in VS due to use of oral anticoagulants.

Conclusions

Spontaneous ITH in patients on oral anticoagulant therapy is a rare event. Nevertheless, anticoagulant therapy is a major risk factor for intratumoral bleeding in VSs and may be associated with higher mortality among patients with ITH in VS and an unfavorable prognosis for recovery of neurological deficits. Vitamin K antagonists were the most common oral anticoagulants in patients with ITH in VS. Microsurgical resection should be pursued as soon as possible in symptomatic patients especially with brain stem compression since resection of the tumor may improve neurological symptoms, decompress the brainstem, and reduce the risk of repeat hemorrhage. Preoperative reversal effect of oral anticoagulants with postoperative coagulation assessment with bridging therapy is mandatory. Discontinuation of oral anticoagulant therapy in elderly patients with risk of falls and VS could be an alternative to surgical treatment.

What Is Already Known on This Topic:

Spontaneous intratumoral hemorrhage in patients on oral anticoagulant therapy is a rare event. Nevertheless, oral anticoagulants are a known risk for intratumoral bleeding in VS and may be associated with higher mortality among patients experiencing this phenomenon. Intratumor bleeding can lead to a rapid and profound onset of symptoms due to the tight and limited confines of the posterior fossa and the immediate expansion of the size of the tumor, which result in severe headache, vomiting, nausea, sudden decline in hearing, and a significantly high incidence of facial weakness. Reports of intratumoral hemorrhage in VS show poor clinical outcomes for patients on anticoagulation therapy, which therefore necessitate recommendations for the use of anticoagulation, especially for withdrawing anticoagulant therapy prior to surgical treatment.

What This Study Adds:

We present the first article in the literature of two cases of patients on oral anticoagulant therapy with intratumoral hemorrhage of VSs and a companion literature review dedicated to this rare phenomenon. After surgery, all neurological deficits for the two patients resolved apart from deafness on the side of the lesion. Our literature review confirmed that patients on oral anticoagulant therapy have an increased risk of intratumoral hemorrhage in VS and poor outcomes that prompt surgical treatment.

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Authors' Contributions: Conception and design: MP and KIA; Acquisition, analysis, and interpretation of data: MP, GD, AA and KIA; Drafting the article: MP, DG and AA; Revising it critically for important intellectual content: MP and KIA; Approved final version of the manuscript: MP, DG, AA and KIA.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Case Report
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An X across the Chest: A Rare Case of a Criss-crossed Sternalis Muscle

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Abstract

Objective. The present case study aims at drawing attention to a very rare presentation of the sternalis muscle noticed during routine dissection, and is intended to highlight the clinical significance and usefulness of this unique muscle in reconstructive surgeries, especially of the breast. **Case Report.** Though many morphological variants of the muscle have been reported, we came across a unique bilateral sternalis muscle during routine dissection for undergraduate medical teaching, in an 80-year-old male cadaver. The muscle originates on both sides from the external oblique aponeurosis from the fleshy belly, and after becoming tendinous, converges in the midline to form a common tendon at the level of the sternal angle, and then splits again into two tendons which become continuous with the ipsilateral sternocleidomastoid. **Conclusion.** Notwithstanding the fact that the presence of a sternalis can be misdiagnosed as a wide range of anterior chest wall lesions and tumors, especially with misdiagnosis of breast masses in routine mammograms, it has great use as a muscular flap for reconstructive surgeries of the anterior chest wall, head, neck and breast.

Key Words: Sternalis Muscle ▪ Mammogram ▪ Breast Augmentation ▪ Submuscular Pocket ▪ Muscular Flap.

Introduction

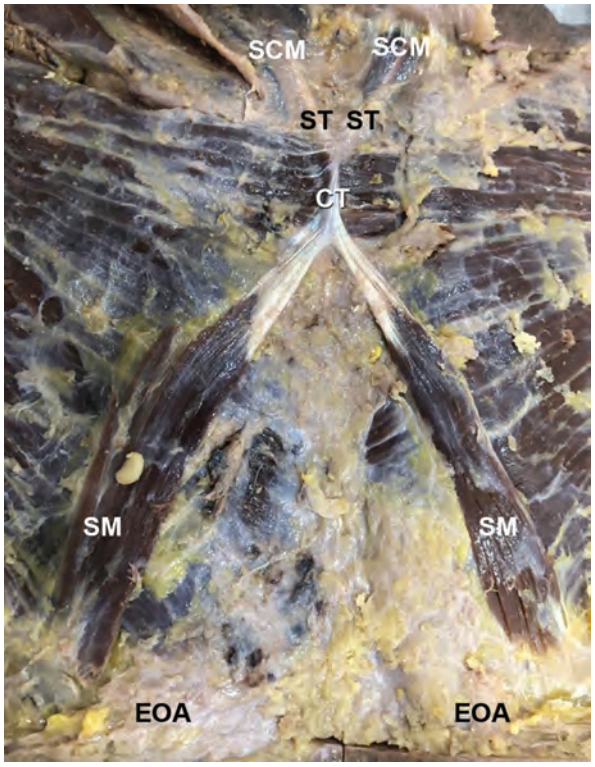
The sternalis muscle (SM) is a well-documented but uncommon muscular variant of the anterior chest wall (1). Since first reported in 1604 by Bartheloney Cabrol, numerous articles have been published on this peculiar muscle, which presents in several morphological forms as a thin or thick band, superficial to the pectoral fascia with longitudinal orientation, either unilaterally or bilaterally, but without any apparent physiological function (1-3).

The sternalis muscle has come to the limelight in recent years because it has been implicated in the misdiagnosis of breast mammograms due to its parasternal location, thus causing confusion amongst radiologists (4), perhaps due to their lack of familiarity with it. However, when undetected before surgical procedures of the thorax, it can interfere with and prolong them (5, 6), but, when detected preoperatively, it can be used as a flap in reconstructive surgeries of the anterior chest wall, breast, head and neck (6, 7), and prevent diagnostic errors and complications during surgical interventions.

Hence, the aim of the present study is to draw the attention of radiologists and surgeons to this very rare presentation of a criss-crossed sternalis muscle, and to discuss further the clinical implications and its usefulness in reconstructive surgeries, especially of the breast.

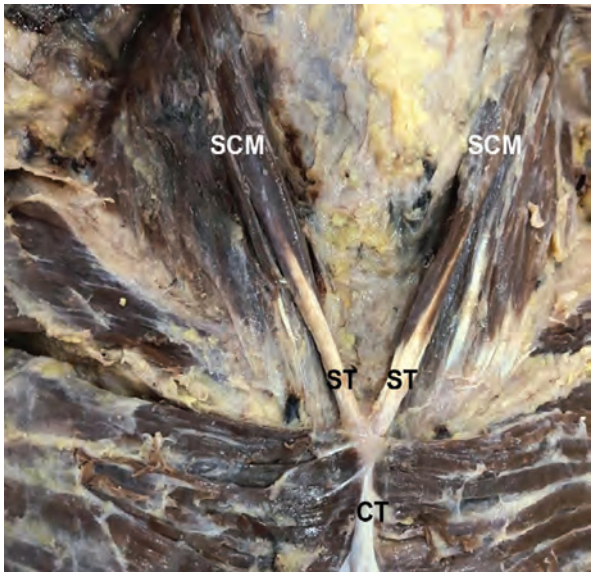
The Case

During routine dissection of the pectoral region for undergraduate medical teaching, an interesting bilateral variation of the sternalis muscle was observed in a 80-year-old male cadaver. The dissection was carried out according to the standard protocol mentioned in Cunningham's Manual of



SCM=Sternocleidomastoid; ST=Split tendons of the sternalis muscle; CT=Common tendon; SM=Sternalis muscle; EOA=External oblique aponeurosis.

Figure 1. Bilateral sternalis muscle with a common tendon in the midline, which splits into two to merge with the ipsilateral sternocleidomastoid.



SCM=Sternocleidomastoid; ST=Split tendons of sternalis muscle; CT=Common tendon.

Figure 2. Common tendon of the bilateral sternalis splitting to merge with ipsilateral sternocleidomastoid.

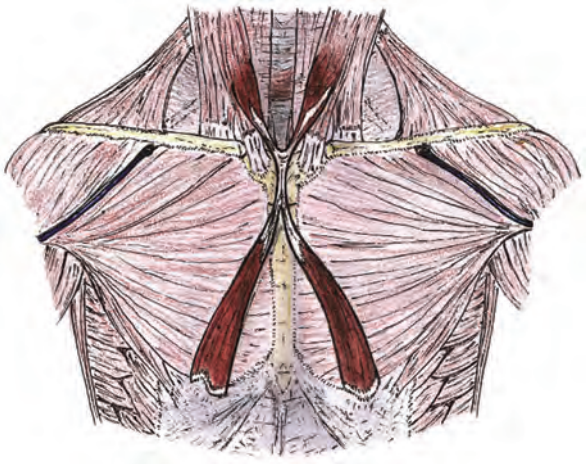


Figure 3. Schematic illustration of the variation.

Anatomy (8). The muscle originated on both sides from the fleshy belly, and was about 12 cm long on the right and 10.5 cm on the left from the aponeurosis of the external oblique muscle, after which it became tendinous, with a tendon about 6.5 cm long on the right and 6 cm on the left. The bilateral muscle converged medially to form a cord-like tendon, 2 cm in length, on the median plane at the level of the sternal angle, which again split into two tendons, to the right (3.5 cm) and left (2.5 cm), after which it became fleshy and blended with the ipsilateral sternocleidomastoid (Figures 1 and 2). The muscles were innervated by medial pectoral nerve on both sides. A schematic diagram of the variation is depicted in Figure 3.

Discussion

With technological advances in medical imaging techniques and the evolution of reconstructive procedures, the sternalis muscle has come into the limelight as a variant worth investigating.

Breast augmentation is one of the top five cosmetic surgical procedures in the world, and has continued to be so since 2006 (9). However, strangely, there were hardly any reports in the literature on the association of this muscle with these procedures until it was highlighted by Khan in 2008 (10), when he came across two cases of SM during breast augmentation procedures. According to him, the absence of reports on the role of this

muscle in augmentation mammoplasty could be due to inadequate anatomic understanding or the lack of visualization when the procedure is performed through a key hole as compared with mastectomies (10). He states that the presence of an SM could be challenging, but of great value during an inframammary approach for breast augmentation procedures, where the prosthesis is placed in the submuscular pocket, deeper than the pectoralis major (1, 10). Although the sternalis can make detection of the dissection plane difficult, as it interferes with dissection of the submuscular pocket (5), it can be used as an extra cover for the implant in the parasternal region, leading to better results, especially in thin individuals in whom the prosthesis may be visible in the lower parasternal region when placed in the submuscular pocket, and hence aesthetically unappealing (10). If a subglandular pocket is used, the implant lies superficially to the musculature, eliminating the concerns raised above (10). However, when a unilateral sternalis muscle is present and a subglandular pocket is used for the prosthesis, without proper dissection of the SM and the medial edge of the pectoralis major, the insertion, as well as the alignment of the implant, can be difficult, leading to asymmetry between the sides, and poor aesthetic outcome (7). According to Kabay et al. (11), inclusion of an SM in mastectomy could depend on its location, the extent of direct invasion by the tumor, and the presence of breast tissue under the muscle. He reported a case of modified radical mastectomy for invasive ductal carcinoma in the presence of an SM, where the sternalis muscle was removed despite not having macroscopic invasion, due to the apprehension that tumor nest cells may be lodged in its lymphatic channels due to the close proximity to the tumor.

In a meta-analysis of the published literature of the last 200 years on the prevalence, and distribution of the sternalis muscle, Asgar et al. (12), reported the worldwide prevalence of SMs to be 6% or 0.06 [0.05-0.7, 95% CI] in 27,470 adults and 0.29 [0.20-0.39,95% CI] in 673 fetuses. The prevalence was three times higher in Asian mongoloids (9.1%) in comparison to Asian Caucasians (3.33%). Cadaveric investigations revealed the overall prevalence of SMs to be 5.96% in adults on the basis of 76 studies, which was higher than in other modalities of investigation such as, multidetector computerized tomography (MDCT) 4.33%, surgical studies 0.47% and mammographic studies, 0.02%, respectively (12).

Although different hypothesis have been proposed regarding the homology of the sternalis, the most widely accepted view is that it is derived from the pectoralis major by virtue of its innervation by pectoral nerves (as in the present case), or from the rectus abdominis due to its innervation by intercostal nerves in many cases (1, 13, 14). It is also hypothesized that the sternalis is a downward extension of the sternocleidomastoid, due to the close association or continuity of their tendons at the clavicle or upper part of sternum, but after a prolonged study of the sternalis, Turner concluded that their relationship is incidental rather than true homology (3).

Many authors have attempted to classify the highly variable anatomy of the SM but the distribution of the sternalis based on classification has been abandoned due to the lack of consistency between the classifications, which failed to reveal any common attributes and characteristics of the SM (12). Although there are reports on the so-called crisscrossed sternalis, our present case is unique and very different from the commonly reported types, with a fleshy origin and insertion, and a crossed tendon in between on the median plane. We reported two cases of SMs earlier, one unilateral, with its origin in the lower part of the pectoral fascia and insertion into the contralateral sternocleidomastoid, and the other a bilateral case with its origin from the external oblique aponeurosis and insertion into the sternocleidomastoid, both origin and insertion being ipsilateral (15).

Conclusion

Although first reported four centuries ago, the SM has remained in relative obscurity due to its erratic occurrence and inconsequential presence. With the technological advancement in medical

imaging and evolution of surgical procedures, the sternalis is increasingly being viewed as a muscle worthy of attention. Awareness of its possible presence could avoid diagnostic errors by radiologists, help surgeons select the most appropriate surgical approach, and it can be made use of in reconstructive procedures, especially when a pocket dissection is made in the subpectoral plane for augmentation mammoplasty.

What Is Already Known on This Topic:

The sternalis muscle is well documented and is familiar to anatomists. Its presence may mislead clinicians and interfere with surgical procedures.

What This Study Adds:

The study highlights a very rare presentation of the sternalis muscle in order to make radiologists, as well as surgeons operating in the area, aware of such a possibility. The muscle has great value as it can be used as a flap in reconstructive surgeries, especially of the head, neck and breast.

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Authors' Contributions: Dissection and identification of the case: SR, IM, NT, RKF and MP; Analysis and interpretation of the case: SR, MP, IM and NT; Drafting the article: MP and SR; Revision of the article critically for important intellectual content: SR and MP; Approved final version of the manuscript: SR, IM, NT, RKF and MP; Schematic diagram of the variation: RKF.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Narrative Review
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George Sclavunos (1869-1954): Anatomical Insights and his contribution into the "Magenstrasse of Waldeyer"

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Abstract
The purpose of this article is to present a well-known physician and highlight his contribution into an essential, but neglected anatomical feature. George Sclavunos (1869-1954) was a 20th century Greek physician, whose scientific work was a significant milestone in global medical knowledge. In 1899 he became Professor of Anatomy and Head Director of the Department of Anatomy. In 1906 Sclavunos G. published the first volume of the three volume book "Human Anatomy" (1906-1926), which is characterized by its unparalleled illustrations. For more than a century it was the most important book of medical literature in Greece. In 1926 he became a Full Member of the Academy of Athens and was named Life Partner of the International Anatomical Society. His interests included Anatomy, Physiology, Histology, as well as Osteology and Syndesmology. In his book "Human Anatomy", he described for first time the "Sialine Groove of the Stomach", which was described by Waldeyer-Hartz almost at the same time as the "Magenstrasse", a German word that means "stomach road". It is a ribbon-like path that extends along the lesser curvature of the stomach from the gastric cardia to the antrum and releases the gastric content directly into the small intestine. Its importance is confirmed by its association not only with drug delivery, but also with anti-obesity surgical techniques. The old German term has come back into common medical usage in view of the commonly performed Magenstrasse and Mill procedure, a form of bariatric surgery. **Conclusion:** Sclavunos G. managed to observe an anatomical structure that has remained of great importance until today.

Key Words: George Sclavunos ▪ Magenstrasse ▪ Stomach ▪ Bariatric Surgery ▪ Biography.

Introduction

George Sclavunos, a distinguished physician of his time, influenced numerous other physicians through his knowledge and anatomical research. By studying his bibliography, it becomes clear that his holistic perception of medicine was what led him to occupy himself with numerous medical domains of his time (1-4). Generally, his field of interest included anatomy, physiology, histology, embryology, osteology and syndesmology (1-3). Throughout his life he was well-known for the numerous books and scientific works he wrote in Greek and German (1, 4-6). Some of them show a familiarity with Galen's works: "On Anatomical Operations", "Medical Terminology", "On the Dissection of Muscles", and "On the Necessity of the Molecules in the Human Body" (4, 5).

Among others, Sclavunos was involved in anatomical research of the human stomach, and in his book "The Anatomy of Man", he described its anatomy thoroughly (1). However, while most of his scientific work is described in detail in published records, little is known about his contribution to the research of the "Magenstrasse". This is a very important but frequently neglected anatomical feature. Its association not only with drug delivery but also with bariatric surgery prompted us to delve deeper into the issue.

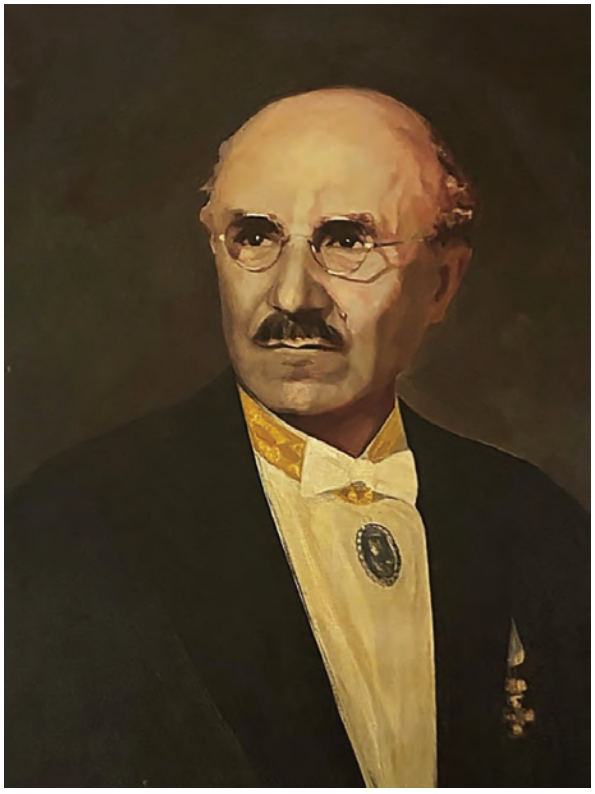

Figure 1. George Sclavunos. Oil painting of Sclavunos G. by an unknown artist. Adapted from the Department of Anatomy of the National and Kapodistrian University of Athens.

The aim of this paper is to shed light on the life and works of a charismatic figure. From our study of his scripts and the bibliography, his significant contribution into the anatomical research of "Magenstrasse" is indisputable.

Sclavunos' Life and Works

George Sclavunos was born in Tithorea on October 16, 1869. He graduated from Thebes School and in the academic year 1884-1885 he enrolled in the Philosophy School of the University of Athens. He then transferred to the Law School. A year later Sclavunos went to Zurich for eight months and later to Würzburg in Bavaria, where he studied Medicine. He graduated in 1891 with a doctorate on the thesis "On elaidin and the keratogenic process of the cardiac fate of the stomach of mammals"(1, 5, 6). In 1891 he passed his practical examinations and worked for two years as an assistant at the anatomical institute of the famous Swiss historian and great anatomist Rudolf-Albert von Köliker in Würzburg (5). He collaborated with the great anatomists Johannes Sobotta, Max Schultze and Hermann Braus, who are the authors of well-known contemporary anatomical textbooks and atlases.

In 1892 he returned to Greece for family reasons. Upon his return to Athens, he was appointed assistant professor of anatomy and curator of the Anatomy department. In 1893 he was appointed as an anatomy lecturer, in 1895 curator of the anatomy laboratory and in 1899-1900 he was elected as a professor and director of the Institute of Anatomy (5, 6). Sclavunos introduced anatomical research and many anatomical terms into the Greek medical literature (4-6). Greek anatomical science began to be comparable to its Western counterpart. In 1906 Sclavunos published the first volume of his monumental three-volume scientific work "The Anatomy of Man" (1). To illustrate his book, he borrowed anatomical paintings from W. Spalteholz, prosector at the University of Leipzig, and histological and anatomical images from J. Sobotta, prosector at Würzburg and later professor at the University of Königsberg and University of Bonn, and O. Schultze, also professor at the University of Bonn. The 48 illustrations in Sclavunos' book were illustrations of his own preparations and they are astonishing in their accuracy of detail. In 1899 he became full professor as the chair of Anatomy and Physiology (5). From the 1933-1934 academic year he was Dean of the Dental School. He retired from the University of Athens in 1938. During his presence at the University he ordered new anatomical casts from abroad while he inaugurated the new Anatomy in Goudi (4, 6).

George Sclavunos used the technique of pyrography to describe the adhesion of muscles to bones by representing the cauterized points which were the points of attachment of the muscles. At that time, the use of the Teichmann technique for injecting a colored substance into corpses was

introduced, and this technique was applied first in Greece and afterwards in Europe (1-4).

He taught Anatomical and Physiological Histology and gave demonstrations with microscopic presentations of embryological preparations, anatomical and histological exercises, as well as anything that had to do with osteology and syndesmology, and taught anatomy courses at the School of Fine Arts (1-3, 5).In 1897 he was elected a life member of the International Anatomical Society and the German Anatomical Society, and from 1926 he was a member of the Academy of Athens. He passed away on May 13, 1954 in Athens (4, 5).

Sclavunos G was married and had four children, including Themistocles Sclavunos, professor of medicine at the University of Athens, and Konstantinos Sclavunos, professor of the Agricultural School of the University of Thessaloniki (5, 6). Last but not least, in 2010, a museum was opened in his honor in Amfikleia. The museum, which bears the name of the late academician, was created jointly by the Municipality of Amfikleia and the School of Medicine of the University of Athens (5, 6).

Sclavunos' Contribution to the Anatomical Research of the Magenstrasse

According to Sclavunos' book "The Anatomy of Man", our internal gastric anatomy is very complex. In particular, the internal surface of the stomach displays folds. In an empty stomach 11 plications are created in total by the contraction of the muscularis mucosae (mucosal plications). Some disappear when the stomach is full and expands, some correspond to pachynsis or strangulation of the muscular coat, and others are created by the retraction of the entire gastric wall (total folds) (1).

Mucosal folds are found circularly from the center of the stomach towards the gastric body, helically and towards the pylorus, in parallel and in a straight line. Their helical construction in the gastric body creates a network of anastomised folds which contributes to the collection of food there. Along the lesser curvature, there are two to four elongated folds independently of one another (non-anastomised), from the heart to the antrum or the pylorus. This anatomical structure was observed in infants by G. Sclavunos and was described in his three-volume book, published in 1906. He named it the "sialine groove of the stomach" (1). Almost at the same time, it was also observed in adults and described by Wilhelm Waldeyer-Hartz (1836-1921). At that time it was believed by anatomists that in animals, water or aqueous food is transported from the heart straight to the antrum or the pylorus, and from there to the small intestine, without admixtures with the remaining content of the stomach. Waldeyer-Hartz decided to write a detailed paper to demonstrate that this phenomenon also happens in human beings. In particular, in 1908 he described how food follows the groove arrangements along the lesser curvature of the stomach, and called this passage the "Magenstrasse" (7). Magenstrasse is a compound word from the German "Magen" meaning stomach and "Strasse" meaning road or street. Therefore, Magenstrasse means stomach road (8).

This gastric tract is shown more clearly through a cross-section of an empty stomach, near the angular incisure (Figure 2). The cavity of the stomach appears to be divided by two folds, in two unequal parts, the upper or gastric tract at the lesser curvature or folds. This is the part which expands when the stomach fills with food content, resulting in the disappearance of the folds. On the other hand, the gastric tract is preserved and the folds remain with the filling of the stomach, advancing the content directly to the small intestine (1).

Apart from the folds, the internal surface of the stomach also shows square or hexagonal eminences. As has been seen microscopically, these eminences are created because the glands which flow into the stomach at intervals and in groups press down on the gastric mucosa towards its inside. These gastric depressions are divided by thin septulums or folds, called gastric ridges. In the pyloric segment of the stomach, the septulums are deeper and the ridges higher, resembling the villi of the intestine. For this reason they are named villous folds (1).

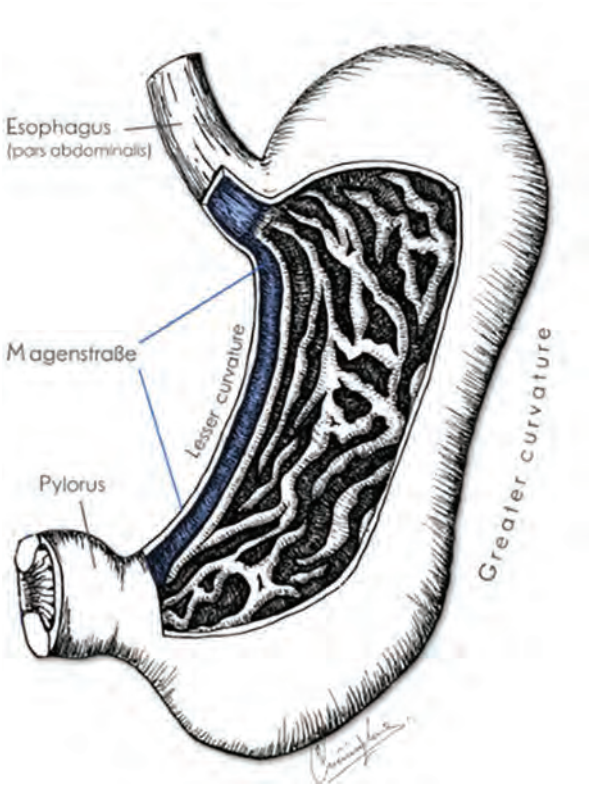

Figure 2. Brief explanation of the Magenstrasse, created by Ioannis K. Antonopoulos.

The empty and relaxed stomach during fasting is shaped like a flattened pipe, with the front wall coinciding with the rear. In contrast, the empty, but contracted stomach during hunger takes the shape of round pipe. During the filling of the empty and relaxed stomach the food goes into it as if entering an empty sack up to the antrum. Inside an empty but systaltic stomach, a bolus encounters resistance because of the cavity created when the front wall falls onto the rear (1).

The human stomach is a multifunctional organ responsible for delivery of nutrients and drugs to the intestines. The digestive gastric process occurs through chemical and mechanical functions, namely, nutrient-stimulated duodeno-gastric reflexes and muscle contractions. There are two types of gastric muscle contractions: the slow volume-reducing contractions of the fundus, and the peristaltic contraction waves in the antrum (ACW). According to the classical description of gastric function, the fundus is a supplier of liquid content to the antrum. The chyme is then mixed, thanks to the action of ACWs, and released into the duodenum. Gastric content released into the upper stomach from the esophagus can take hours to enter the small intestine. This happens because the content stored in the fundus is delivered to the antrum from above and then empties from the antrum into the duodenum. In contrast to the traditional description of gastric emptying, a new path was discovered which was none other than the "stomach road", or "Magenstrasse" that Sclavunos first described (9).

Many years later, Li et al. examined the mixing and emptying of gastric content in the human stomach using a Computational Fluid Dynamics (CFD) method, in order to understand the Magenstrasse phenomenon better. Their study also confirmed the existence of a fast pathway close to the lesser curvature of the stomach. This result is in accordance with the study by Pal et al. (9, 10).

However, as Li et al. first observed, this phenomenon does not occur when gastric contents with different properties are mixed. In contrast, a retropulsive flow is produced, by a terminal antral contraction (TAC), that leads the food contents to the proximal antrum. This contributes to the mixing of water with light gastric contents, but not with the heavy ones, and as a consequence, layers of different food contents are created. In particular, this phenomenon is produced thanks to the gastric motility, the high viscosity of the content and the food matrix that is created by heavier gastric contents. Due to the higher viscosity, gastric wrinkles and food matrix show lower resistance in water than in light gastric contents. In addition, it is impossible for the gastric contents to fill the gastric wrinkles completely. Thus, flow resistance in the food matrix is higher than in the gastric inner surface. Consequently, water is forced to empty immediately near the gastric inner surface trough the Magenstrasse (10).

The Magenstrasse and Drug Delivery

As previously outlined, the importance of the Magenstrasse is clear, regarding the pharmacokinetic

properties of various drugs. For this reason, researchers have tried to study this phenomenon thoroughly. On the basis of the studies by Winter et al. and Kiyota et al., the Magenstrasse is of great importance for drug absorption in humans who are being fed, as it represents a shortcut through the fed stomach and carries fluids rapidly allowing the rapid onset of drug plasma levels (11, 12).

The importance of this road was also confirmed by Grimm et al., who conducted an MRI study to demonstrate that gastric emptying of water, in a fed state clinical trial, was as fast as under fasting conditions (13).

Processes such as secretion, digestion, and gastric emptying occur at the same time in the postprandial stomach. Thanks to the Magenstrasse, water is emptied rapidly within 15–45 min from the stomach, even under postprandial conditions. As a result, this road may have essential consequences for the drug plasma concentrations after fed-state administration of immediate release medications. If a drug is taken under postprandial conditions with water, the direct increase of drug plasma concentration is likely to occur, similar to fasting conditions. This observation clearly reflects the presence of the Magenstrasse. In particular, it means that the drug is rapidly transported to the small intestine, through the gastric road, without losing time by mixing with gastric contents. In the case of pain medication for example, where we desire immediate results, this road seems quite useful. Undoubtedly, gastric emptying in fasting and postprandial conditions is quite difficult to study. For this reason, in 2019 Schick et al. developed a simulation model, the GastroDuo, to examine the presence of the stomach road and predict the in vivo performance of oral drugs. According to their experiments, there is clear association between the drug plasma concentrations and the gastric emptying of dissolved and undissolved medications (14).

Kilian et al. conducted a study in humans with radiolabelled paracetamol to assess gastric emptying in fasted and fed conditions. Unexpectedly, the absorption of paracetamol was similar between the pre- and post-prandial state, or even faster in the fed state. The authors hypothesized that this reflected the Magenstrasse phenomenon, suggesting that the fast dissolution of paracetamol occurred at the top of the stomach, and paracetamol moved along the Magenstrasse with the liquid content of the stomach directly into the duodenum (15).

One year later, this model was used by the same investigator in order to examine the performance of a fast disintegrating and dissolving Aspirin® tablet (FDDT) under fasted and fed conditions, and compare it to a regular Aspirin® tablet (RT) administered in the fed state. The FDDT showed faster drug release and improved emptying kinetics in the GastroDuo. The early tmax observed for the FDDT under fed conditions could be related to the presence of the Magenstrasse. Thanks to this road, the drug is released rapidly when it is co-administered with water. In contrast, drug release from the RT resulted in later tmax, because it was insufficient to allow gastric emptying via the Magenstrasse. Therefore, this work highlights the biopharmaceutical significance of the Magenstrasse for oral drug therapy (16).

This result is definitely in accordance with the study by Vrbanac et al. They mention that in the postprandial stomach, fast emptying of ingested liquids is accomplished thanks to this road and this definitely has an impact on the therapeutic onset of co-administered drugs. The motor activity of the fasted stomach is carried out in cycles (MMC), characterized by fluctuation of the muscle contraction intensity. Different intensities of motility patterns can have an influence on the disintegration time and distribution of a drug and the formulation of particles within the various stomach regions (17).

Paixao et al. created a mass transport model (MTM) that reflects drug distribution along the different regions of the stomach as a consequence of random dosing relative to the different contractile phases of the migrating motor complex (MMC). According to this model, drug distribution along the different regions of the stomach can result in the inhomogeneous (i.e., not well mixed) presence of the drug in the stomach. This depends on the time of administration relative to the MMC

phase. To capture the drug concentrations (in particular phenol red) in the different segments of the GI tract both in fasted and fed state conditions, it was essential to include a bypass flow compartment. This bypass road is the Magenstrasse, and it facilitates the transport of the drug directly to the duodenum (fasted state) or antrum (fed state) (18). It is also worth mentioning, that the study by Henze et al. showed that the Magenstrasse phenomena reported in humans, may also occur in landrace pigs (19).

The Magenstrasse and Bariatric Surgery

In parallel, the importance of the Magenstrasse was also confirmed by its association with bariatric surgery. Obesity is a worldwide epidemic and, over time, numerous types of anti-obesity procedures have been described. One of the first surgical techniques was Vertical Banded Gastroplasty (VGB). Biliopancreatic diversion with a duodenal switch (BPD/DS) was an additional procedure for food restriction and ulcer reduction (20).

In general, anti-obesity techniques should not only be effective in weight loss, but also safe, with minimal side-effects and metabolic sequels. Johnston et al. tried to evolve a simpler type of gastroplasty in order to satisfy these criteria. They described the Magenstrasse and Mill procedure (M&M), which was first carried out in 1987 in England (20). In this operation, a long narrow stomach tube (namely, the Magenstrasse) is formed around a bougie, and the stomach is stapled and divided from the incisura angularis to the angle of His. Unlike the previous techniques, it does not leave foreign material within the abdomen (21). It was generally shown that this procedure achieves acceptable weight loss, while preserving gastric emptying mechanisms and thus minimizing possible side-effects, such as vomiting, dumping and diarrhea (22). Moreover, Carmichael et al. showed that the M&M operation reduces levels of plasma leptin, and improves the fibrinolytic activity, factors that are associated with morbid obesity and coronary heart disease (22, 23).

In order to reduce severe gastrointestinal and hydroelectrolytic disturbances, surgeons adopted the Roux-en-Y gastric bypass (RYGB). The RYGBP horizontal pouch is better than the RYGBP vertical pouch, because fewer marginal ulcers have been reported after this procedure. This happens because, as Berger first described in 1934, the proximal Magenstrasse contains many more parietal cells than the fundus (24). A technically less demanding operation that gained rapid acceptance was Sleeve Gastrectomy (SG). According to this technique, a circular opening is created in the stomach at the junction between the corpus and the antrum. The stapling then progresses along the small gastric curvature and a tubular pouch, similar to a sleeve, is created (20). 80% of normal stomach is actually resected and this leads to restriction and a decrease in ghrelin levels, and significant weight loss (25). This procedure could be performed safely laparoscopically with satisfactory results (20).

In 2016, Bessemans et al. compared the efficacy of three procedures in obese patients: RYGB, SG and M&M gastroplasty. Their study showed that classical SG provides almost similar results to RYGB and appears to be slightly better than the M&M procedure (26). In addition, three years ago, an interesting experimental study with rabbits was conducted by Sümer et al. in order to compare the SG with the M&M gastroplasty. It was found that weight loss was achieved with the first method, whereas weight did not decrease with the second. M&M leaves the large curvature of the stomach in place. Since the connection between the tube and the large curvature remains open, it can be considered that food also accumulates there, which hinders the restrictive function (27). SG was actually an evolution of the M&M procedure, and is the most popular anti-obesity operation nowadays. Perhaps its success is not purely due to the surgical technique, but especially due to the part of the stomach that remains, which is none other than the Magenstrasse.

Conclusion

To conclude, George Sclavunos was undoubtedly a great Greek physician and professor of his time, whose work contributed to the gradual formation of the foundations of modern anatomy science. His field of interest was extensive and among others, he described the "stomach road", a tubular portion of the stomach, which is a route favored by fluids. Waldeyer-Hartz described it almost at the same time and named it the Magenstrasse. Although it is an anatomical feature that is frequently neglected, its importance is indubitable, in relation not only to drug delivery, but also anti-obesity surgical techniques. We suggest that further studies are required for a more extensive understanding of its function.

What Is Already Known on This Topic:
There are articles regarding the Magenstrasse and its association with drug delivery and different bariatric surgery techniques.

What This Study Adds:
In the existing literature, there is nothing written about George Sclavunos and his contribution to knowledge about the Magenstrasse. We suggest that it is wise to consider the work of men like him. For this reason, the scope of our article is double. First, to present this distinguished physician and secondly, to underline the overall importance of the Magenstrasse. Moreover, this anatomical feature might be the reason of the success of Sleeve Gastrectomy, which is the most common bariatric surgery today.

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The Genesis of Multidisciplinary Health Professionals Teams for Pain Management. A History from the Hellenic Antiquity to Modern Palliative Medicine

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Abstract
The aim of our article is to highlight the history of pain management. The multidisciplinary team (MDT) concept in confronting pain was first conceptualized by the Hippocratics, and has evolved through time and become a trend in medicine over recent decades. Documentary research was conducted to unveil the story of the evolution of MDTs. From the early 1950's the idea of an MDT approach to deal with various types of pain was sporadically introduced in medicine. Studies encouraged health institutions to support this concept by providing health professionals with training, alongside the necessary facilities and resources. Specialized care programs started with Dame Cicely Mary Strode Saunders as one of the pioneers. **Conclusions.** Team work and continuous interdisciplinary treatment of pain have rendered MDTs essential for health systems. Barriers in flexibility, information flow and personal issues give rise to the need for better organization and training. Pain and terminal disease palliation call for MDTs, and educated leaders to run them. Present and future health MDTs are considered necessary in all medical fields.

Key Words: Interdisciplinary Treatment ▪ Hospice ▪ Pain ▪ History of Medicine.

Introduction

The multidisciplinary team (MDT) concept is defined as a unit of health care professionals who specialize in various different scientific fields and work collaboratively together. This team usually cares for multiple patients. However, each patient receives continuous individualized attention from every team member. The great majority of studies concerning MDTs have demonstrated better results for those patients who use their programs, in contrast to patients under a single physician's care (1).

The MDT concept seems to have originated within the Corpus Hippocraticum, as the Hippocratics advocated a holistic care approach to their patients. Physicians, therapainides (nurses) and psychologists wanted both body and soul homeostasis to be achieved (2). Many centuries later, thousands of warriors and pilgrims were killed during the First Crusade and the Pope issued directives to various Chivalric Orders, such as the Hospitallers and Templars, to create facilities for lodging and medical care, and thereby created the first centers organized for MDT work. One must keep in mind that the term "hospes" originally meant "hospitality" (3). From that time, the MDT concept of caring for the sick and dying took hold, with the formation of various religious orders across Europe, under the patronage of priests and monks in hospitals, churches and monasteries. Meanwhile, charitable institutions also appeared, under municipal jurisdiction (4–5). Modern medicine realized that the MDT concept constitutes a realistic, holistic, applicable and optimum concept.

This narrative review aims to record the history of the creation of MDT care for patients suffering from all kinds of pain.

The Early 20th Century and MDT Origins

From the early 20th century various centers appeared which were specialized in the management of one kind of pain. Thus, headaches, backaches, cancer pain, spinal lesion pains and others were dealt with as separate entities. However, the need for a holistic approach to patients led to a more complete health concept. The Sicilian-American anesthesiologist John Joseph Bonica (1917–1994) was the first to understand that traumas suffered during the Word War II may cause chronic pain of a variety of etiologies, and that veterans could not easily find comfort or organized pain management facilities. Thus, he was the first to propose such activities and is considered as the physician who first introduced pain management as a medical specialty. Also, he published the treatise "The Management of Pain" in 1953, describing pain as "the most complex human experience, in my view." His own MDT Pain Clinic, which included specialists from eight disciplines, was intended to be a model for others. However, he struggled to organize these centers, and only succeeded in establishing pain clinics offering limited options for pain on a form of multidisciplinary basis, known as "Pain Clinics". (6–8).

During the 1950s some health centers appeared worldwide organized at first as anesthesiology centers, and they operated as day-care clinics which had the capacity to care for 8 to10 patients with pain of nonmalignant and malignant origin (9). Nurses, as caregivers demonstrating empathy, soon suggested they should be appointed as members of such teams (10). The idea of a MDT of physicians seems to have been suggested by insurance companies in the 1930s as they required a complete and thorough diagnosis of any health issue, in relation to insurance issues (11).

A National Mental Health grant sponsored five working conferences between 1951–1952 on interdisciplinary teams (12). The word "hospice" was defined as a term in 1951 as an autonomous, centrally administrated, medically directed program, providing a continuum of home, outpatient and homelike inpatient care for terminally ill patients and their families. It employs an interdisciplinary team (13). Nevertheless, we should not forget that the first attempt to comprehend the need for such a team is to be found in psychiatry (13, 14) and pediatric medicine.

The American State Children's Bureau took an initial step towards the development of interdisciplinary teams in 1918. Those teams were supported by pediatricians, appropriate medical specialists, and therapists, nurses and social workers. The team of specialists used techniques originating in psychiatry, psychology and sociology (15). In the late 1950s, pain clinics were included in university facilities, pain specialists were trained, diagnostic tools and scoring scales were created, symptom control teaching methods appeared, and home care was introduced (16). It was the era when MDTs for pain palliation were considered to be in vogue. Their success was both health and socially related, and complete among the health system users (17).

Luski wrote the first book on MDTs in 1959, describing their benefits and limitations, while noting various team training techniques (12). It was the American professor of anesthesiology Henry Knowles Beecher who during 1950's made the strongest claim for anesthesiology as the sole discipline of pain, not only of pain management but of pain research as well. Although he had collaborated with colleagues from internal medicine, pharmacology, and psychology, he had failed to find in the complexity of pain a compelling argument for a multidisciplinary approach and in that way to help the formation of MDTs (8).

At the beginning of the 1960s, various publications appeared in favor of MDTs, encouraging health institutions to support this concept by providing facilities and resources. Specialized care programs and trained health professionals should be included, as most studies of the era noted (18). In 1958, Dame Cicely Saunders, shortly after she qualified, wrote an article arguing for a new approach to end-of-life care and pain. She emphatically wrote, "It appears that many patients feel deserted by their doctors at the end. Ideally the doctor should remain the center of a team of

professionals who work together to relieve where they cannot heal, to keep the patient's own struggle within his compass and to bring hope and consolation to the end" (19). The 1960's were also characterized by the work of the professor in anesthesiology, Bill Fordyce and the professor in anesthesiology and neurological surgery, John Loeser. They embraced a model of treatment focusing on fighting the symptoms and introducing functional restoration techniques (6). Bonica understood the significance of Fordyce's work and invited him to become a participant in the MDT at his Pain Clinic. Fordyce's program remained part of Rehabilitation Medicine and was not incorporated into the pain clinic until 1978. Fordyce believed that pain eradication was a secondary goal and he mainly taught individual patients ways to control and maintain their pain at a tolerable level (8). Nevertheless, the problems of establishing pain clinics continued due to inadequate funding to support the initial high costs, the lack of time to train and improve the skills for the clinic staff, and the absence of a unifying model of pain care. Those factors led to the fact that the initial success was followed by the slow growth of pain clinics (6).

Saunders and MDTs in the Modern Era

Dame Cicely Mary Strode Saunders (1918–2005) was an English nurse, social worker, physician and prolific writer, who changed the medical world's opinion regarding pain and MDT work. She was among the first to realize that the sensation of pain involves both the body and the mind or soul. Nociceptive (visceral and somatic) and neuropathic, acute or chronic, real or phantom, pain needs to be confronted in all its aspects, and requires care for the sick, their relatives, caregivers, and the MDT itself (20). Thus, Saunders introduced the idea of "total pain," which included the physical, emotional, social, and spiritual dimensions of the distress felt (17). In 1967, Saunders founded St Christopher's Hospice in south-west London, and its philosophy soon became the catalyst for the development of MDTs. Soon after St Christopher's Hospice began admitting patients, she wrote in one of her papers, "It became obvious that this new approach to end-of-life care should not be regarded as the model but rather as a demonstration of principles that could be interpreted variously in different cultures and settings" (21, 22).

Magno Josefina Bautista was the next important figure who broke ground in helping medical professionals comprehend the need for pain relief and palliative care for terminally ill patients. She formed the American Academy for Hospice and Palliative Medicine, the National Hospice Foundation, and the International Hospice Institute. Within these organizations she played a critical role during the following decades in educating people and health professionals about the merits and benefits of physician-based MDTs and hospice care. Pain confrontation and MDTs were then related, and palliative medicine changed forever (23).

Modern era MDTs meet regularly to elucidate their course of actions and offer an opportunity to the members to share examples of good practice and share their opinions. Thus scientific communication is considered an essential element of pain palliation and the core of a collective process in relation to the patient (24). The personal, individually tailored, multimodal therapy provided by an MDT is widely suggested to be critical for pain management (25). MDTs, or virtual MTDs networking to achieve results, in the modern era use outsourcing, including private social workers, neighborhood pharmacists and clergy. MDT networking provides opportunities to interact between various MTDs, and even promote the creation of a central team for a 24-hour response (26). This group of specialists, the MDT, is nowadays considered the gold standard worldwide. There are reports connecting MDTs and pain palliation with overall survival, making MDTs an independent prognostic factor (27).

The new millennium started with an emphasis on pain management through MDTs. In the USA the decade 2000-2010 was designated as the "Decade of Pain Control and Research", elevating pain management to the level of one of the most significant causes of health. This action alone

greatly enhanced public awareness of pain, and the related research advanced the understanding of chronic pain mechanisms and improved treatment pathways (6).

Obstacles to MDTs and the Future

The key to the proper functioning of MDTs in the 21st century is to have professionals working together and learning from each other during their practice. Although the interdisciplinary exchange of opinions in creating a care plan is emphasized, patients experience poor communication and interpersonal conflicts as obstacles to medical care (28). Recent studies have shown that MDT reform is acknowledged to be a complex but important medical process. Meanwhile, medical personnel need training and require support during the process (29). Surprisingly, longitudinal care is considered for some an obstacle that needs to be overcome by MDTs, related to the cost of services (30). By definition, MDTs should redeem their human capital in order to produce the best care results (31).

However, during the last decade of the 20th century MDTs faced considerable issues in truly coping with their declining patients' conditions (32). As living "organisms", MDTs should remained active in research, able to conduct clinical trials, and ready to analyze beneficiaries' opinions and emotions in order to improve outcomes for all their patients. Studies have shown that patient-reported outcome measures improve MDTs' insights, to help them confront their patients' problems and symptoms better, and provide improved results. It is essential to encourage patient engagement and empowerment in MDTs, as an interconnection which should improve patient satisfaction and outcomes. The future of personalized medicine most probably belongs to MDTs (33). In the last century, the MDT concept was anthropocentric, based on the most important people involved. Somewhere in this equation lies the key to future good MDT leaders who are essential for maintaining patient safety and the evolution of MDTs (34).

Conclusion

MDTs were introduced during Hellenic antiquity, were used throughout the ages, and formed in modern medicine from the early 1960s. Obstacles do exist, but the function of MDTs represents a natural evolution in medical care, reflecting all the advances made by different disciplines and health professionals, and proposing the use of multiple modalities of treatment, patient palliation and support for caregivers.

What Is Already Known on This Topic:
Pain management is a field of modern medicine, dealt with mainly in palliative care.

What This Study Adds:
This study highlights the historical background of the concept of pain management, especially its roots in ancient times and its diachronic historical root.

Authors' Contributions: Concept and design: HK and LA; Acquisition, analysis and interpretation of data: HK and LA; Drafting the article: HK, LA, EM; Revising it critically for important intellectual content: HK, LA, EM. Approved final version of the manuscript HK, LA and EM.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Response to Letter to the Editor by Josef Finsterer, MD, PhD: "The More Intensive the Diagnostic Workup, the More Likely It Is That the Cause of Coccygodynia Can Be Clarified"

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Key Words: Coccygodynia ▪ Coccygeal Disc Disease ▪ Perianal numbness.

Dear Editor-in-Chief

We have read the letter to the editor from J. Finsterer (1) with great interest. We are grateful for his insightful comments. In our case (2), we initially and importantly highlighted that the main causes of pain in the coccygeal region remain unclear.

We agree with the importance of various alternative conditions that might lead to coccygodynia. Concerning the first limitation mentioned, we have already expressed that the specific pathophysiological mechanisms related to coccygodynia are still vague. Moreover, this situation may be related to a plethora of possible causes or disorders. Apart from this, we noted that the pain may be related to lumbar spine degeneration (3, 4), but in our patient the symptoms were not associated directly with the lumbar region, since mild tenderness was localized at the sacrococcygeal joint. Concerning the beneficial role of physiotherapy in such conditions, the literature has recorded a wide variety of treatment options for coccygodynia management (5). Additionally, in the limitation section, we already noted that our patient was unable to complete the MRI scan due to discomfort, and only sagittal views were available. The third limitation referred to the perianal numbness. This symptom might arise from the irritation of the coccygeal plexus or its branches, which supply the coccyx, the sacrococcygeal joint, and the skin over the coccyx. Furthermore, no cerebrospinal fluid examination was performed in our patient. Concerning the fifth limitation, in the discussion section, we pointed out that the pathophysiological pathway of coccygodynia remains complex and multifactorial. Also, the appropriate diagnosis of this condition is clinical, relying primarily on history and physical examination, and it should be investigated thoroughly. Under these circumstances numerous of specialists could be implicated.

Finally, the sixth limitation, regarding specific imaging studies, wasalready discussed in the limitation section, and we indicated that no static or dynamic lateral films, provocative discography or dynamic MRI were performed.

We thank Dr. Finsterer for his valuable and insightful comments, adding his significant experience in this manuscript.

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ODOBRENE INDIKACIJE: Istovremeno samo s acetilsalicilnom kiselinom (ASK) ili s ASK-om uz klopidogrel ili tiklopidin za prevencija aterotrombotskih događaja u odraslih pacijenata nakon akutnog koronarnog sindroma (AKS) s povišenim srčanim biomarkerima. Istovremeno s acetilsalicilnom kiselinom (ASK) za prevenciju aterotrombotskih događaja u odraslih pacijenata, koji imaju bolest koronarnih arterija (BKA) ili simptomatsku bolest perifernih arterija (BPA) s visokim rizikom od ishemijskih događaja.

KONTRAINDIKACIJE: Preosjetljivost na aktivnu supstancu ili neku od pomoćnih supstanci. Aktivno, klinički značajno krvarenje. Lezija ili stanje, ako se smatra da nosi značajan rizik od većeg krvarenja. Istovremeno liječenje bilo kojim drugim antikoagulansom, osim u specifičnim situacijama kad se mijenja antikoagulacijska terapija ili kad se nefrakcionirani heparin daje u dozama potrebnim za održavanje otvorenog centralnog venskog ili arterijskog katetera. Istovremeno liječenje AKS-a antitrombocitnom terapijom u pacijenata s prethodnim moždanim udarom ili tranzitornom ishemijskom atakom (TIA). Istovremeno liječenje BKA/BPA primjenom ASK-e u pacijenata s prethodnim hemoragijskim ili lakunarnim moždanim udarom ili bilo kojom vrstom moždanog udara unutar posljednjih mjesec dana. Bolest jetre povezana s koagulopatijom i klinički značajnim rizikom od krvarenja, uključujući pacijente s cirozom jetre, Child-Pugh stadija B i C. Trudnoća i dojenje.

POSEBNA UPOZORENJA I MJERE OPREZA: Tokom cijelog perioda liječenja, preporučuje se kliničko praćenje u skladu s antikoagulantnom praksom. Preporučuje se pažljiva primjena u stanjima s povišenim rizikom od krvarenja, a primjena RIVERA mora se prekinuti ako se pojavi teško krvarenje. Oprezno primjenjivati u pacijenata s klirensom kreatinina od 15 - 29 ml/mm, a oprez se preporučuje u pacijenata s umjereno oštećenom funkcijom bubrega (klirens kreatinina od 30 - 49 ml/min), koji istodobno primaju druge lijekove koji povećavaju koncentraciju rivaroksabana u plazmi. Kada je s klirensom kreatinina <15 ml/mm, ne preporučuje se primjena lijeka. U pacijenata s malignim neoplazmama s visokim rizikom od krvarenja, primjena rivaroksabana je kontraindicirana. Rivaroksaban se ne smije primjenjivati za tromboprofilaksu u pacijenata koji su nedavno podvrgnuti transkateterskoj zamjeni aortnog zaliska. Upotreba lijeka se ne preporučuje pacijentima koji u anamnezi imaju trombozu, a dijagnosticiran im je antifosfolipidni sindrom. Ako je potreban invazivni postupak ili hirurški zahvat, lijek se mora prestati uzimati najmanje 24 sata prije zahvata, ako je to moguće i na temelju kliničke procjene ljekara. Ozbiljne kožne reakcije povezane s primjenom rivaroksabana, uključujući Stevens-Johnsonov sindrom/toksičnu epidermalnu nekrolizu i reakciju na lijek s eozinofilijom i sistemskim simptomima, DRESS sindrom, prijavljene su tokom praćenja nakon stavljanja lijeka u promet. Pacijenti s rijetkim nasljednim poremećajem nepodnošenja galaktoze, nedostatkom „Lapp laktaze" ili glukoza-galaktoza malapsorpcijom, ne bi trebali primjenjivati ovaj lijek.

NEŽELJENA DJELOVANJA: Anemija, omaglica, glavobolja, krvarenje u oko, hipotenzija, hematom, epistaksa, hemoptiza, krvarenje iz desni, krvarenje u gastrointestinalnom traktu, bolovi u gastrointestinalnom traktu i abdomenu, dispepsija, mučnina, konstipacija, proljev, povraćanje, povišene transaminaze, svrbež, osip, ekhimoza, kožno i potkožno krvarenje, bol u ekstremitetima, krvarenje u urogenitalni sistem, oštećena funkcija bubrega vrućica, periferni edem, smanjenje opšte snage i energije, postproceduralno krvarenje, kontuzija, sekrecija iz rane.

DOZIRANJE I NAČIN UPOTREBE: Akutni koronarni sindrom (AKS): Pacijenti koji uzimaju RIVER, u dozi od 2,5 mg dvaput na dan, moraju također svakodnevno uzimati dozu od 75-100 mg ASK-e ili dnevnu dozu od 75-100 mg ASK-e uz dodatak dnevne doze od 75 mg klopidogrela ili standardne dnevne doze tiklopidina. Liječenje treba redovno procjenjivati za svakog pojedinog pacijenta, važući rizik od ishemijskih događaja nasuprot rizika od krvarenja. O produženju liječenja preko 12 mjeseci potrebno je odlučiti za svakog pacijenta pojedinačno, jer je iskustvo primjene do 24 mjeseca ograničeno. Bolest koronarnih arterija (BKA) ili simptomatsku bolest perifernih arterija (BPA): Pacijenti koji uzimaju RIVER, u dozi od 2,5 mg dvaput na dan, također trebaju uzimati ASK, u dnevnoj dozi od 75-100 mg. U pacijenata kod kojih je uspješno provedena procedura revaskularizacije donjeg ekstremiteta (hirurškim ili endovaskularnim zahvatom, uključujući i hibridne procedure) zbog simptomatske BPA, liječenje ne treba započeti prije nego što se postigne hemostaza.Trajanje liječenja kod svakog pojedinog pacijenta treba odrediti na temelju redovnih kontrola i treba uzeti u obzir rizik od trombotskih događaja nasuprot rizika od krvarenja.

BH.RIV.2023.01.

Za sve detaljnije informacije o lijeku koristiti posljednji odobreni Sažetak karakteristika lijeka i Uputstvo o lijeku.

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