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Contents

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Journal of Interdisciplinary Medicine

Aims and scope

The Journal of Interdisciplinary Medicine aims to publish top quality papers related to any fields of medicine that present an interdisciplinary dimension.

The journal will mainly focus on recent advances in the field of diagnosis and treatment of the most common situations encountered in the clinical or research practice. Interdisciplinary approaches will be extremely welcomed, presenting new advances in the approach of different pathologies from the perspective of various clinical fields.

The Journal of Interdisciplinary Medicine will publish high-quality basic and clinical research related to interdisciplinary medical fields, in a common approach that will integrate the clinical studies with the pre-clinical work dedicated to the discovery of new mechanisms involved in the development and progression of a large spectrum of diseases.

The journal will try to provide the entire medical community with the perspective of the regional specifics of Central and Eastern European countries. The journal will primarily focus on publishing original research papers, but also other types of materials (such as review articles, case reports, state-of-the-art papers, comments to editor, etc) will be extremely welcomed.

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FROM THE EDITOR

JIM at the Interface Between Two Healthcare Systems

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The year 2020 has been a real challenge for many systems of our society, and especially for the healthcare system. The COVID-19 pandemic impacted health, economy, tourism, transport, hospitality industry, and many others.[1] From the perspective of a medical care provider, this pandemic has changed the way we practice medicine.

On one hand, there was a dramatic decrease in the proportion of patients with different emergencies (other than COVID-19) who presented to the hospitals, due to fear from the new coronavirus. To a certain extent, people started to consider hospitals dangerous places instead of locations providing safety and health, and preferred to stay home even though they were aware of the risk of lacking appropriate care.[2] At the same time, a significant number of medical practitioners became infected by the SARS-CoV-2 virus, and some of them died, even at a young age, raising a serious alerting signal for the medical community.[3] In several countries, the healthcare system was close to collapse as a result of a very high number of critical cases requiring mechanical ventilation and insufficient infrastructure in the intensive care units.[4] At the same time, several countries faced the challenge of many medical practitioners resigning, leaving the system in deficit at the level of its most precious resource – the qualified human force.

This sanitary crisis will for sure change the way we practice medicine in the future. One of the most probable directions of development is the field of telemedicine applications and digital medicine. This new type of medicine reduces the direct contact between the doctor and the patient and allows remote monitoring of patients with known diseases, avoiding the risk of viral contamination for the doctor and the patient. This is a significant paradigm shift from traditional medicine, which was based on physical consultation associated with modern technology for diagnosis and treatment. The healthcare system based on face-to-face interaction between the patient and the physician starts to be replaced by a new healthcare system, based on digital interaction.[5] However, not all diseases may be diagnosed via telemedicine, some of them requiring advanced imaging techniques for which the physical presence of the patient is mandatory. This is also the case for many diseases requiring interventional or surgical treatment.

In the attempt to reflect the current trends in the field of interdisciplinary medicine, starting with 2021, the Journal of Interdisciplinary Medicine will give

the highest priority to articles addressing new applications of telemedicine and digital medicine that may represent a significant step forward in the current revolution of healthcare forced by the COVID-19 pandemic. These articles will be subject to an expedited review using a dedicated fast-track system and will be followed by invitations for editorial comments using social media channels. Starting with the first issue of 2021, JIM will introduce its new *Inter-DIGI* platform, which will integrate the articles, reviews, and comments on topics related to digital applications of interdisciplinary medicine. By this, we aim to align our efforts with the ones of the entire medical community in the fight against the devastating COVID-19 pandemic, at the same time keeping our readers updated with the current progress of innovative applications in medical technology.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Kaushal V, Srivastava S. Hospitality and tourism industry amid COVID-19 pandemic: Perspectives on challenges and learnings from India. Int J Hosp Manag. 2021;92:102707.
2. World Health Organization. Attacks on health care in the context of COVID-19. https://www.who.int/news-room/feature-stories/detail/attacks-on-health-care-in-the-context-of-covid-19 (15 December 2020)
3. Dabholkar YG, Sagane BA, Dabholkar TY, Divity S. COVID 19 Infection in Health Care Professionals: Risks, Work-Safety and Psychological Issues. Indian J Otolaryngol Head Neck Surg. 2020;72:1-6.
4. Tiruvoipati R, Botha J. Fighting a pandemic with mechanical ventilators. Intern Med J. 2020;50:1019-1020.
5. Kichloo A, Albosta M, Dettloff K, et al. Telemedicine, the current COVID-19 pandemic and the future: a narrative review and perspectives moving forward in the USA. Fam Med Community Health. 2020;8:e000530.

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REVIEW

SURGERY // ONCOLOGY

Trends in Oncology: an Updated Review of Minimally Invasive Surgery vs. Traditional Open Surgery

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ABSTRACT

Objective: To review the recent trends in methodology for the most frequent oncological surgeries. More specifically, this paper will compare the minimally invasive methods to the conventional open method. It aims to find out whether minimally invasive surgeries are feasible treatments for certain types of cancers. **Methods:** A review of retrospective studies searched in PubMed, Cochrane Library etc. was used to identify the studies published on this topic within a period of 6 years. Oncologic outcomes, postoperative complications/outcomes, and intraoperative outcomes were the main variables in the comparison to the surgical methods under review. **Conclusion:** Despite the recent controversy with minimally invasive surgery being contraindicated for cervical cancer, it is still an acceptable method for other types of common cancers. However, there are limitations to the approach, and the surgeon should make a prudent selection between minimally invasive and open surgery depending on the type of tumor and patient characteristics. Further studies, especially with randomized control trials, must be conducted.

Keywords: surgery, minimally invasive, oncology, review

INTRODUCTION

In recent years, there has been controversy over whether or not minimally invasive surgery (MIS) should remain the gold standard for many surgical procedures, in particular, for radical hysterectomies. The issue was brought to light by two studies in The New England Journal of Medicine, which established that minimally invasive radical hysterectomy was associated with a lower disease-free survival rate than open surgery.[1,2] For a number of years, the National Comprehensive Cancer Network (NCCN) guidelines have stated that robotic radical hysterectomies were the recommended approach for patients with cervical cancer, citing the benefits of such an approach.[3] However, it seems that with the shocking revelation of the dangers of minimally invasive hysterectomies, surgeons should reevaluate their methodology of choice for other surgical procedures as well. Thus, in accordance with what may be a rapid and prema-

ture adoption of robotics in the field of medicine, an updated review is needed to evaluate the efficacy of MIS in the treatment of other oncological diseases and determine what should be the gold standard method.

Foundational Information on MIS

MIS emerged in the 1980s to create a safer and more effective form of surgery compared to traditional open surgery. It was designed to meet the surgical needs of many patients. MIS can commonly be separated into three forms: laparoscopic surgery, endoscopic surgery, and robotic surgery.[4] Laparoscopic surgery is performed through one or more small incisions, using small tubes, tiny cameras, and surgical instruments. Endoscopic surgery is a diagnostic and therapeutic procedure performed through the body's organs and vessels. Robotic surgery is a magnified, 3D view of the surgical sites to help the surgeon operate with precision, flexibility, and control. It has recently become quite prevalent as it resulted in smaller incisions and shorter hospital stay. It has also been attributed to lower risk compared to that of traditional open surgery, with a reduction of operative traumatic damage.

Public View on MIS

From the surgeons' perspective, MIS is less preferred than open surgery. However, that may be different from the public view of MIS. As John Wickham stated in 1987, "Surgeons applaud large incisions and denigrate keyhole surgery. Patients, in contrast, want the smallest wound possible, and we at Britain's first department of minimally invasive surgery are convinced that patients are right."[5] The patients definitely prefer MIS as it usually results in shorter hospital stay, smaller incision, and smaller scars. According to a study by Haws *et al.*, patients are very heavily swayed by long-term outcomes, surgeons' recommendations, and risk of complications for both open surgery and MIS. The majority of patients were convinced that open surgeries are more painful (83.8%), have an increased risk of complications (78.5%), increased recovery time (89.3%), and increased costs (68.1%).[6] Overall, especially for spinal surgery, MIS is perceived by patients as a more suitable and better option than open surgery.

Methodology

The sources that we used to compile our data were The Cochrane Library, Pubmed, The New England Journal of Medicine, and PLOS ONE. We compiled a list of the most frequent operating room procedures and the most common types of cancers, and from the overlap, we determined the final list of surgeries for this study. Then, we compared search results for "open surgery vs. laparoscopic surgery" and found the top results (must have had more than 5 results in the last 5 years). The search terms used were: "open," "laparoscopic," "minimally invasive," and "surgery."

We included papers based on meta-analyses in our review. Some papers were based on a compilation of data from a number of relevant studies. Other papers were based on empirical data or direct case studies.

The main factors that were considered in determining which surgical method was more feasible were: intraoperative outcomes, oncologic safety, postoperative outcomes, and postoperative recovery. Miscellaneous factors were also considered if they were deemed to be significant to the studies under review. We have omitted some studies that were either too outdated (before 2014) or questionable in their accuracy (based on individual case studies). Study results derived from an insufficient number of study groups were omitted for a more accurate and precise analysis. Results comparing laparoscopic vs. robotic surgery with no open control were omitted. Cholecystectomy was also omitted because there were not enough oncological results.

ANALYSIS OF MIS VS. OPEN SURGERY IN DIFFERENT TYPES OF CANCERS

Hepatectomy

Compared to laparoscopic gastrectomies, there are more studies available for laparoscopic hepatectomies. This is because laparoscopic liver resection was already widespread decades ago. Thus, the laparoscopic approach for liver resection is not a novel procedure but rather part of the standard guidelines for surgery.

In 2014, the 2nd International Consensus on Laparoscopic Liver Resection had constituted MIS to be the standard method of treatment (IDEAL 3) for low-risk or minor hepatectomy. However, they defined MIS for major hepatectomies (resection of more than 3 segments) to still be innovative (IDEAL 2b). There were not enough high-quality studies conducted to push MIS to be the standard method for all types of hepatectomies.[7]

Three years later, 2,819 patients participated in a large, multi-institutional study that compared MIS to the open approach for major hepatectomies.[8] This study was significant because it was the largest one yet to collect data on

minimally invasive major liver surgeries with an open control. Although the result did not immediately confer absolute confidence to the advocates of MIS for high-risk surgeries, it did show a sort of optimism for the approach. The conclusion was that MIS was not worse than open surgery for patients with large tumors (one-sided 95% CI <1.02).

Not long after that, the first randomized controlled study had been conducted comparing laparoscopic and open liver resection.[9] The trial included 280 patients with resectable liver metastases and found that the post-operative complication rate was significantly lower for the laparoscopic group (19% vs. 31%). The study is in definitive support of laparoscopic liver surgery and is evidence enough that it should be continued to be implemented in the field. Furthermore, a recent compendium of case studies (n = 233) showed the success of major laparoscopic resection.[10]

In conclusion, it is generally agreed that minor hepatectomies should be performed laparoscopically. In addition, while the approach for major hepatectomies should be determined based on the skill of the surgeon, the difficulty of the surgery, and patient condition, it could very well prove to be the more favored method in the near future.

Pancreaticoduodenectomy

A 2016 study conducted by Zhang *et al.* compared laparoscopic pancreaticoduodenectomy (LPD) and open pancreaticoduodenectomy (OPD).[11] The study examined whether LPD (a subset of minimally invasive PD) is as safe and feasible as OPD, assessing the improvement in R0 resection after LPD. PD has always been a complex procedure due to the dissection around important vessels and three complex reconstructions. The major difference between the two PDs were significantly reduced blood loss and blood transfusion requirement with LPD compared to OPD, and a shorter postoperative stay (6 days vs. 9 days).

However, there are some studies that refute the possibility of LPD leading to a faster rate of R0 resection, and therefore, it was concluded that LPD cannot be considered a significantly "better" procedure than OPD. It was also suggested that there is a learning curve for LPD. As a consequence, higher morbidity and mortality were associated with LPD at the beginning of the learning curve.[12] Nevertheless, given the clear-cut benefits of less blood loss and shorter postoperative stays, LPD proves to be a safer and more feasible method for patients.

The same study also looked at the feasibility of pancreaticoduodenectomy, compiling all studies conducted between January 1994 and November 2013. During the compilation of the evidence to assess the benefits of laparoscopic procedures, the authors looked for wound infection, length of operation time, intraoperative blood loss, risk of complications, length of hospital stays, and overall oncologic outcomes. The study determined that there was a reduction in wound infection due to the minimally invasive approach, but the laparoscopic procedures have taken longer during operation because of their complexity and the lack of experience of surgeons. Some of the difficulties in pancreaticoduodenectomy were partly due to the difficulty in access and exposure of the pancreas, difficulty in hemorrhage control from major vasculature, and difficulty in reconstruction of biliary and pancreatic remnants. However, procedure complexity has largely been alleviated by the development of surgical robotics. This advancement led to significantly shorter operation times for minimally invasive pancreaticoduodenectomy (MIPD): 444 ± 93.5 minutes vs. 559 ± 135 minutes with OPD. The study also determined that there was a significant reduction in blood loss, lower risk of complications, shorter hospital stay, and overall better oncologic outcomes. It concluded that due to its advantages, MIPD is worthwhile. The complexity of MIPD has been alleviated and will continue to become better through advancements in surgical robotics and more experienced surgeons in the future.[12]

Esophagectomy

Two studies were carried out to determine whether minimally invasive esophagectomy (MIE), or even hybrid minimally invasive esophagectomy (HMIE), should replace open procedures for esophageal cancer. The first study determined that HMIE and MIE yielded shorter hospital stays due to the lower number of excised lymph nodes.[13] There were also lower rates of pulmonary complications and anastomotic leaks, as well as better outcomes in the MIE groups in certain situations. However, MIE had longer operation times, and survival benefits were similar in OE and MIE. In addition, there was a longer learning curve for MIE due to the highly advanced laparo-thoracoscopic skills required. The first study concluded that although there are clear benefits to MIE and HMIE over OE, longer learning curves and longer operating times due to procedure complexity of the procedure make it hard for minimally invasive surgery to be used more widely. For esophageal cancer, MIE and HMIE should be used only in high-volume, experienced university surgical centers. Another study based on 13,267 patients who had esophageal cancer determined that there were similar short- and

long-term survival rates between hybrid, minimal, and open procedures.[14] The study demonstrated that in-hospital mortality was reduced in MIE (3% for MIE vs. 4.6% for open surgery), and the risk of pulmonary complications was reduced in MIE (17.8% for MIE vs. 20.4% for open). However, there wasn't an apparent reduction of morbidity or mortality in the MIE group compared with the open esophagectomy group. In addition, there was no significant difference in the rate of anastomotic leaks after esophagectomy between the two groups.

Adrenalectomy

Regarding adrenalectomies, MIS is the general method of choice. As of 2013, laparoscopic adrenalectomy has been recommended for benign adrenal tumors (≤6 cm in diameter and weighing <100 g). For tumors greater than 6 cm, there is an ongoing debate between endocrinologists regarding the surgical method. In a study conducted by Conzo *et al.* in 2015, when laparoscopic adrenalectomy (LA) and open adrenalectomy (OA) were performed for lesions >10 cm, the recurrence rate was 50% and 42%, respectively.[15] LA was contraindicated in the presence of intravenous thrombus and infiltration of structures. It was noted that an increased risk of peritoneal carcinomatosis after LA was a concern; however, results regarding that specific postoperative risk were inconclusive.

But in 2018, another study showed that the laparoscopic approach was acceptable regardless of tumor size and without any associated risk increase.[16] The study followed 28 patients with 31 adrenal tumors. Tumor sizes were categorized into <5 cm and ≥5 cm in diameter. No difference for mortality and recurrence rate between LA and OA was found.

Furthermore, in a 2017 study investigating lateral retroperitoneoscopic adrenalectomy (LRA) versus OA (n = 67, all tumors were greater than 5 cm; 41 patients by LRA and 26 patients by OA), the risk of local recurrence and peritoneal carcinomatosis, a highly associated risk, were found to be comparable for the two approaches.[17]

Taking all above studies into consideration, the interpretation is that for larger adrenal tumors, LA is acceptable but technically demanding, as it has been observed that LA requires longer surgery time. However, this review focuses not on intraoperative factors but postoperative results, so the length of surgery time will be considered negligible when evaluating feasibility. Thus, the relevant issue is which minimally invasive approach, laparoscopic anterior versus endoscopic posterior, will produce better results.

Gastrectomy

Gastric surgery is one of the most relevant fields for MIS but there are no international guidelines set in place that dictate when and for what type of disease it is indicated. The current gold standard for gastric surgery is the open method. Currently, there are several relevant, ongoing multicenter trials, and results are pending. Unfortunately, data availability along with updated clinical standards have not kept up with the technical advances in the field.

In a case-control study comparing robotic gastrectomy (RG), laparoscopic gastrectomy (LG), and open gastrectomy (OG),[18] intraoperative blood loss was shown to be significantly lower in the LG (95.93 ± 119.22 mL) and RG (117.91 ± 68.11 mL) groups compared to the OG (127.26 ± 79.50 mL, p = 0.002). The length of hospital stay was shorter for LG and RG, and there was no difference in complication rates regardless of the tumor type. It has shown that the main benefit of MIS is a significantly faster post-surgical recovery rate. A 2017 study has evaluated the effects of laparoscopic distal gastrectomy (LDG) and found that there were fewer pulmonary complications. The mortality rate was similar between the two groups (0.4% for LDG vs. 0% for ODG, p = 0.249), and the 5-year survival rate was also similar (95.9% for LDG vs. 94.9% for ODG).[19]

For early gastric cancer, LDG is comparable to OG. The general consensus across all recent studies is that there is not enough data to conclusively state the feasibility and safety of LDG for advanced gastric cancer. Studies are still ongoing (particularly to confirm the benefit of the laparoscopic method in elderly patients with advanced gastric cancer), and there is a lack of high-level clinical evidence.[20,21] Currently, a randomized controlled trial studying the efficacy of laparoscopic subtotal gastrectomy for advanced gastric cancer is being carried out in Korea.[22] Totally laparoscopic complete gastrectomy (TLCG) has been performed successfully for advanced gastric cancer proving its feasibility, but it faces the steep wall of being technically challenging. Furthermore, oncological results have yet to be recorded.[23] Laparoscopic gastrectomy continues to evolve due to its touted benefits, technological improvements, and increasing experience of surgeons. Although there are multiple studies regarding the minimally invasive routes, further studies are needed to evaluate the oncological safety of these procedures.

Colorectal Cancer

One of the studies regarding the trends of minimally invasive surgical resection for colorectal cancer was con-

ducted on May 16, 2019, based on The Florida Inpatient Discharge Data Set. The study examined the clinical data of patients who underwent elective surgery for colorectal cancer between 2013 and 2015. A total of 10,513 patients were analyzed, of which 5,451 had open surgery, 4,403 had laparoscopic surgery, and 659 had robotic surgery. The rate of MIS increased from 46.95% to 48.72% in the study period, and among a variety of minimally invasive procedures, the use of robotics increased from 9.82% in 2013 to 15.48% in 2015.[24] This upward trend in MIS for colorectal cancer shows the popularity of MIS among the general public. Another study, a meta-analysis, explored the overall effect and safety of anterior laparoscopic surgery versus conventional open surgery for patients with colorectal cancer based on 24 randomized controlled trials, with 4,592 patients in the laparoscopic group and 3,865 patients in the open surgery group. Laparoscopic surgery had significantly less blood loss, shorter hospital stay, and lower rates of postoperative mortality and postoperative complications. However, one benefit of open surgery was that laparoscopic surgery had statistically higher operative times than open surgery. The study concluded that despite the shorter operative times for open surgery, laparoscopic surgery was far superior for colorectal cancer due to its major benefits.[25]

Another study aimed to determine the feasibility of conducting laparoscopic colorectal resection in elderly patients, as very old patients with colorectal cancer are at a high risk of mortality. This study compiled previous studies from PubMed, Medline, Embase, and Google Scholar and examined primary determiners, such as 30-day mortality rates, 30-day morbidity rates, and secondary determiners, such as operating time, time to oral diet, number of retrieved lymph nodes, blood loss, and 5-year survival rates. Elective laparoscopic resection had a mortality rate of 2.92% and a morbidity rate of 23%. The study found significant differences between laparoscopy and open surgery, demonstrating reduced morbidity in the laparoscopic group. In addition, the study determined that laparoscopic surgery patients were more likely to have shorter hospital stays and shorter time to oral diet. The authors concluded that laparoscopic surgery was safer and more feasible than open surgery for patients over the age of 85.[26]

Patients with liver cirrhosis are also at a high risk for colorectal surgery because the safety and effectiveness of laparoscopy in colorectal surgery involving cirrhotic patients is not clear. A study performed in 2018 concluded that laparoscopic colorectal surgery is a safer and less invasive alternative to open surgery in some cirrhotic patients, leading to less blood loss, earlier recovery, and less additional harm in terms of postoperative complications or long-term oncological outcomes.[27]

Lung Cancer

There is no dispute that lung cancer is a leading cause of death in the world, and the management of the disease remains one of the most important topics in the medical field. The minimally invasive method for lung cancer surgery is termed video-assisted thoracoscopic surgery (VATS), and it has already been established as being just as effective as open surgery. Currently, there is no large dispute on this matter, and there have been multiple studies worldwide (e.g., Sweden, Taiwan, United States) proving the adequacy of VATS.[28–30] Long-term survival for both minimally invasive and open surgery was equal, while postoperative complications for the former were less frequent.

According to a 2019 study, there has been a significant increase in the number of VATS performed for non-small-cell lung carcinoma (NSCLC) in the U.S. (study limitations: patients were all ≥65 years of age, the number of VATS may have increased secondarily to an increase in the number of diagnoses/resections).[31] There was a 39% increase from 2006 to 2014 in VATS carried out in patients who had elected to undergo surgery. However, there was a significant regional variation regarding the management of the disease. Unlike in the case of other cancers where the type of tumor indicated the course of treatment, the staging of the lung cancer was not a factor in the variation of treatment (VATS vs. open). In response to this discrepancy, a number of medical practitioners are advocating for VATS to become the official standard method of treatment so that it can be adopted universally in all hospitals.

Thyroid Cancer

Head and neck surgeries are usually the most technically demanding interventions because of the general anatomy of the tumors' location. Because thyroid cancer has a high incidence in women, surgeons also consider the cosmetic outcome when performing the procedures. Hence, more surgeons are choosing the minimally invasive approach. However, it requires a specific skill set, may also have higher risks associated with it, and it remains controversial.

One of the most recent meta-analyses comparing endoscopic thyroidectomy (ET) and open thyroidectomy (OT) showed that the two methods were comparable in terms of post-surgical results.[32] The study took into account some of the most common complications for thyroidectomy such as damage to the recurrent laryngeal nerve and post-

operative hypoparathyroidism; transient recurrent laryngeal nerve palsy occurred more frequently in ET. Also, the study showed that completeness of thyroid resection may be lower in case of ET because patients were reported to have comparatively higher serum thyroglobulin (sTg) levels. However, there was not enough postoperative data to make a conclusion about sTg levels because there was no significant difference between ET and OT when it came to tumor recurrence rates.

All studies comparing other types of endoscopic thyroidectomies, such as minimally invasive video assisted thyroidectomy (MIVAT) and robotic thyroidectomy, with the conventional method reached the conclusion that ET was comparable to OT.[33–36] Other studies have shown that not only was MIVAT as safe as open surgery, it may also have beneficial immunosuppressive effects through the downregulation of TNF-α.[37] Also, there are new risks posed by robotic surgery brachial plexus neuropathy and tracheal injury.[38]

For the minimally invasive method, whether it is MIVAT or robotic surgery, there is a strict learning curve which prevents the application of more innovative methods in a wider setting. Endoscopic methodologies and techniques represent one of the prominent current topics in endocrinology. For the time being, there are limitations set in place for ET, and for higher risk patients OT is the preferred method, but hopefully this will change with continued interest and further studies.

Prostate Cancer

As prostate cancer is one of the most common types of cancer in men, it has long been debated whether prostatectomy should be performed through laparoscopic or open procedures. A randomized, controlled study of men recently diagnosed with localized prostate cancer examined the functional and oncological postoperative outcomes up to 24 months after laparoscopic or open surgery. The study included 308 men aged between 35 and 70 years, 151 of which were treated with open radical retropubic prostatectomy, while 157 were treated with robot-assisted laparoscopic prostatectomy. The study did not find significant differences between open and laparoscopic surgery regarding urinary and sexual function, the proportion of biochemical recurrences, or the proportion of patients who had imaging evidence of progression. The authors concluded that laparoscopic surgery and open surgery yielded similar functional outcomes at 24 months. The benefits of a robotic approach to prostate cancer would largely be related to its minimally invasive nature.[39]

Another study assessed the effects of laparoscopic radical prostatectomy or robotic-assisted radical prostatectomy compared to open radical prostatectomy in 446 randomized participants with clinically localized prostate cancer. The authors examined primary outcomes, such as prostate cancer-specific survival, urinary quality of life, and sexual quality of life, and secondary outcomes such as biochemical recurrence-free survival, overall survival, overall surgical complications, serious postoperative surgical complications, postoperative pain, hospital stay, and blood transfusion. The study determined that there was no difference between laparoscopic surgery and open surgery in urinary and sexual quality of life, and little to no difference in overall surgical complications and serious postoperative complications. The study also concluded that laparoscopic and robotic procedures are very slightly better in terms of postoperative pain at one day and up to one week. However, there was no significant difference in postoperative pain at 12 weeks. It was also determined that robotic procedures may reduce the length of hospital stay, and both robotic and laparoscopic procedures would result in 68 fewer blood transfusions per 1,000 men compared to open procedures. The study concluded that there was no clear evidence that laparoscopic and robotic procedures would have better oncological outcomes that the open counterpart. The differences between the procedures were minimal to non-existent, all of which were not persuasive evidence to the superiority of laparoscopic procedures. Taking into account the possibility of the surgeon's lack of experience in minimally invasive surgery, as of right now, prostate cancer should be treated through open procedures.[40]

DISCUSSIONS AND CONCLUSIONS

Reviewing the results of the relevant studies from the past five years, we found that there was an overwhelming amount of data that emphasizes the efficacy of MIS. In many areas, the endoscopic or robotic method has already been adopted as the standard for low-risk surgeries. With the exception of cervical cancer, prostate cancer, and disseminated cancers, there is a definite accelerating trend towards MIS compared to a decade ago.

MIS is safer and more feasible for appendectomies. As for pancreaticoduodenectomy, there are clear benefits that make MIE a better option for most patients. However, there is a need for further research on the long-term outcomes of MIPD. There is a very long learning curve for esophagectomies due to the complexity of the procedure. The studies conducted on esophagectomies require fur-

ther improvements in surgical devices and surgeon experience. MIS is the method of choice for adrenalectomies, but is restricted to certain tumor sizes. Further studies are needed regarding gastrectomies, and open surgery continues to be the recommended method for prostate cancer. For all other oncological surgeries, MIS is accepted as a feasible treatment but is restricted by the type and grade of the disease.

For the most part, MIS is only comparable/not superior to open surgery, meaning that postoperative complication rates, tumor recurrence rates, and other factors were not significantly different. It was rare to find a paper that reviewed MIS to be the better method of choice without the addendum that further studies were needed to assess long-term risks. Also, if the cancer had progressed to a stage where the tumors were large or disseminated, MIS was contraindicated because resection would not be as complete as with open surgery. The limitations of MIS are also based upon the skills of the surgeon and availability of instruments. Even when it is considered feasible, the surgeon must consider the various endoscopic approaches from different anatomical sites; this remains a topic of controversy and requires further study.

In conclusion, an increasing number of surgeons are choosing the minimally invasive method, and the current trends show that this approach is largely accepted in the medical community.

CONFLICT OF INTEREST

Nothing to disclose.

REFERENCES

1. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *N Engl J Med*. 2018;379:1895-1904.
2. Melamed A, Margul DJ, Chen L, et al. Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. *N Engl J Med*. 2018;379:1905-1914.
3. National Comprehensive Cancer Network. NCCN. http://www.nccn.org/about/news/ebulletin/ebulletindetail.aspx?ebulletinid=1569 (09 September 2020)
4. Minimally invasive surgery. Mayo Clinic. Mayo Foundation for Medical Education and Research; 2019. http://www.mayoclinic.org/tests-procedures/minimally-invasive-surgery/about/pac-20384771 (09 September 2020)
5. Schlich T, Tang CL. Patient choice and the history of minimally invasive surgery. *The Lancet*. 2016;388:1369-1370.
6. Narain AS, Hijji FY, Duhancioglu G, et al. Patient Perceptions of Minimally Invasive Versus Open Spine Surgery. *Clin Spine Surg*. 2018;31:E184-E192.
7. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg*. 2015;261:619-629.
8. Thornblade LW, Shi X, Ruiz A, Flum DR, Park JO. Comparative Effectiveness of Minimally Invasive Surgery and Conventional Approaches for Major or Challenging Hepatectomy. *J Am Coll Surg*. 2017;224:851-861.
9. Fretland ÅA, Dagenborg VJ, Bjørnelv GMW, et al. Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. *Ann Surg*. 2018;267:199-207.
10. Cho W, Kwon CHD, Choi JY, et al. Impact of technical innovation on surgical outcome of laparoscopic major liver resection: 10 years' experience at a large-volume center. *Ann Surg Treat Res*. 2019;96:14-18.
11. Zhang YH, Zhang CW, Hu ZM, Hong DF. Pancreatic cancer: Open or minimally invasive surgery? *World J Gastroenterol*. 2016;22:7301-7310.
12. Qin H, Qiu J, Zhao Y, Pan G, Zeng Y. Does minimally-invasive pancreaticoduodenectomy have advantages over its open method? A meta-analysis of retrospective studies. *PLoS One*. 2014;9:e104274.
13. Wallner G, Zgodziński W, Masiak-Segit W, Skoczylas T, Dąbrowski A. Minimally invasive surgery for esophageal cancer – benefits and controversies. *Kardiochir Torakochirurgia Pol*. 2014;11:151-155.
14. Zhou C, Zhang L, Wang H, et al. Superiority of Minimally Invasive Oesophagectomy in Reducing In-Hospital Mortality of Patients with Resectable Oesophageal Cancer: A Meta-Analysis. *PLoS One*. 2015;10(7):e0132889.
15. Conzo G, Pasquali D, Della Pietra C, et al. Laparoscopic adrenal surgery: ten-year experience in a single institution. *BMC Surg*. 2013;13Suppl2:S5.
16. Mohammed A, Amine H, Atiq SE, et al. Applicability and outcome of laparoscopic adrenalectomy for large tumours. *Pan Afr Med J*. 2018;31:23.
17. Chen W, Lin W, Han DJ, Liang Y. Lateral retroperitoneoscopic adrenalectomy for complicated adrenal tumor larger than 5 centimeters. *Afr Health Sci*. 2017;17:293-300.
18. Parisi A, Reim D, Borghi F, et al. Minimally invasive surgery for gastric cancer: A comparison between robotic, laparoscopic and open surgery. *World J Gastroenterol*. 2017;23:2376-2384.
19. Hu Y, Huang C, Sun Y, et al. Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. *J Clin Oncol*. 2016;34:1350-1357.
20. Li Z, Shan F, Ying X, Xue K, Ji J. Laparoscopic versus open gastrectomy for elderly local advanced gastric cancer patients: study protocol of a phase II randomized controlled trial. *BMC Cancer*. 2018;18:1118.
21. Son T, Hyung WJ. Laparoscopic gastric cancer surgery: Current evidence and future perspectives. *World J Gastroenterol*. 2016;22:727-735.
22. Hur H, Lee HY, Lee HJ, et al. Efficacy of laparoscopic subtotal gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer: the protocol of the KLASS-02 multicenter randomized controlled clinical trial. *BMC Cancer*. 2015;15:355.
23. Shinohara T, Hanyu N, Tanaka Y, Murakami K, Watanabe A, Yanaga K. Totally laparoscopic complete resection of the remnant stomach for gastric cancer. *Langenbecks Arch Surg*. 2013;398:341-345.
24. Osagiede O, Spaulding AC, Cochuyt JJ, Naessens J, Merchea A, Colibaseanu DT. Trends in the Use of Laparoscopy and Robotics for Colorectal Cancer in Florida. *J Laparoendosc Adv Surg Tech A*. 2019;29:926-933.
25. Song XJ, Liu ZL, Zeng R, Ye W, Liu CW. A meta-analysis of laparoscopic surgery versus conventional open surgery in the treatment of colorectal cancer. *Medicine (Baltimore)*. 2019;98:e15347.
26. Devoto L, Celentano V, Cohen R, Khan J, Chand M. Colorectal cancer surgery in the very elderly patient: a systematic review of laparoscopic versus open colorectal resection. *Int J Colorectal Dis*. 2017;32:1237-1242.
27. Zhou S, Zhu H, Li Z, Ying X, Xu M. Safety of laparoscopic resection for colorectal cancer in patients with liver cirrhosis: A retrospective cohort study. *Int J Surg*. 2018;55:110-116.
28. Al-Ameri M, Bergman P, Franco-Cereceda A, Sartipy U. Video-assisted thoracoscopic versus open thoracotomy lobectomy: a Swedish nationwide cohort study. *J Thorac Dis*. 2018;10:3499-3506.
29. Wang BY, Huang JY, Lin CH, et al. Thoracoscopic Lobectomy Produces Long-Term Survival Similar to That with Open Lobectomy in Cases of Non-Small Cell Lung Carcinoma: A Propensity-Matched Analysis Using a Population-Based Cancer Registry. *J Thorac Oncol*. 2016;11:1326-1334.
30. Ezer N, Kale M, Sigel K, et al. Outcomes after Video-assisted Thoracoscopic Lobectomy versus Open Lobectomy for Early-Stage Lung Cancer in Older Adults. *Ann Am Thorac Soc*. 2018;15:76-82.
31. Phillips JD, Bostock IC, Hasson RM, et al. National practice trends for the surgical management of lung cancer in the CMS population: an atlas of care. *J Thorac Dis*. 2019;11(Suppl4):S500-S508.
32. Chen C, Huang S, Huang A, et al. Total endoscopic thyroidectomy versus conventional open thyroidectomy in thyroid cancer: a systematic review and meta-analysis. *Ther Clin Risk Manag*. 2018;14:2349-2361.
33. Zhang P, Zhang HW, Han XD, Di JZ, Zheng Q. Meta-Analysis of Comparison Between Minimally Invasive Video-Assisted Thyroidectomy and Conventional Thyroidectomy. *European Review of Medical and Pharmacological Sciences*. 2015;19:1381-1387.

34. Li Y, Zhou X. Comparison between endoscopic thyroidectomy and conventional open thyroidectomy for papillary thyroid microcarcinoma: A meta-analysis. *J Can Res Ther*. 2016;12:550-555.
35. Tan Z, Gu J, Han Q, et al. Comparison of Conventional Open Thyroidectomy and Endoscopic Thyroidectomy via Breast Approach for Papillary Thyroid Carcinoma. *Int J Endocrinol*. 2015;2015:239610.
36. Cho MJ, Park KS, Cho MJ, Yoo YB, Yang JH. A comparative analysis of endoscopic thyroidectomy versus conventional thyroidectomy in clinically lymph node negative thyroid cancer. *Ann Surg Treat Res*. 2015;88:69-76.
37. Zheng C, Liu S, Geng P, et al. Minimally invasive video-assisted versus conventional open thyroidectomy on immune response: a meta analysis. *Int J Clin Exp Med*. 2015;8:2593-2599.
38. Caruso G, Spinosi MC, Cambi J, Passali FM, Bellussi L, Passali D. Open versus robotic thyroidectomy: is it really a controversial choice? *Kulak Burun Bogaz Ihtis Derg*. 2015;25:375-376.
39. Coughlin GD, Yaxley JW, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. *Lancet Oncol*. 2018;19:1051-1060.
40. Ilic D, Evans SM, Allan CA, Jung JH, Murphy D, Frydenberg M. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. *Cochrane Database Syst Rev*. 2017;9:CD009625.

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MINI REVIEW

PUBLIC HEALTH // EPIDEMIOLOGY

Examination of Air Pollution's Relationship with COVID-19, Physical and Mental Health

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ABSTRACT

Air pollution is a result of natural phenomena or human activities that can cause the release of harmful substances in the environment, leading to adverse health outcomes among living beings. Pollution is associated with adverse health impacts on multiple organ systems among humans. While the respiratory and cardiovascular systems are mainly affected, there are other health issues related to the eyes, skin, brain, blood, immunity, behavioral/mental well-being, and reproduction among exposed individuals. Air pollutants can especially have higher health impacts on people at the extremes of their ages (children and elderly) and on those suffering from underlying respiratory and heart issues. Pollutants such as ozone, sulfur dioxide, particulate matter, and nitrogen dioxide have respiratory effects among children and adults and are associated with increased respiratory diseases, asthma exacerbations, and related hospitalizations. Carbon monoxide interferes with transporting oxygen by forming carboxyhemoglobin leading to cardiovascular, neurological, and respiratory problems. Particulate matter is a heterogeneous mixture of tiny particles of varying compositions found in the atmosphere and has a wide variety of severe health effects. Particulate matter emits from combustion, diesel engines, power generation, and wood-burning, and certain industrial activities. Lead is considered neurotoxic and has more severe consequences among children. Here we summarize characteristics of six criteria air pollutants and associated air quality risk assessment parameters known as the Pollutant Standard Index (PSI). The present manuscript also examines the impact of air pollution on human behavior, mental well-being, and neurological health consequences, as air pollution has been associated with cognitive decline, hyperactivity, dementia, anxiety, depression, aggression, and Alzheimer's disease-related changes. Lastly, we also attempt to look into any relationship between air pollutants and Coronavirus disease (COVID-19) and examine its possible association with a higher COVID-19 incidence, complications, and mortality.

Keywords: particulate air pollution, adverse health effects, human health, COVID-19, environmental health, Pollutant Standard Index

BACKGROUND

Air pollution is the presence of harmful substances due to natural phenomena or anthropogenic activities in the environment that can have detrimental health consequences on humans when exposed.[1,2] Air pollution is categorized into outdoor (ambient) and indoor types.[1,2] According to the World Health Organization (WHO), 9 out of 10 individuals are inhaling polluted air, which results in millions of deaths each year.[2] Here we explore the impacts of air pollution on human behavior, mental well-being, and neurological health consequences while summarizing characteristics of six criteria air pollutants and associated parameters known as the Pollutant Standard Index (PSI). Furthermore, we also attempt to look into any relationship between air pollutants and Coronavirus disease (COVID-19).

TYPES, MECHANISM, AND COMMON HEALTH IMPACTS

There is already clear proof that both short- and long-term ambient air quality changes are correlated with elevated mortality and morbidity among adults and children.[3,4] Six air pollutants including carbon monoxide, sulfur dioxide, lead, particulate matter, ozone, and nitrogen oxides (nitric oxide and nitrogen dioxide) all are associated with adverse health occurrence among exposed individuals (Table 1).[5–8] The PSI is a generally used risk assessment parameter derived from the ambient concentration of the major air pollutants.[9] The PSI can be used to assess air pollution levels from 0 to 500, values above 100 being considered unhealthy.[9]

In household settings or indoors, air pollution is associated with fuel combustion (appliances, heating, stove etc.), tobacco use, building materials, household cleaning chemicals, heating/cooling systems, and pesticides.[10] Inadequate ventilation or movement of outdoor pollutants into indoor spaces can further deteriorate air quality.[10] Indoor (household) pollution has been linked to higher lung cancer risk, especially when houses are not well ventilated, coal is used for household activities, and the residence is located near industrial areas.[11–13] In outdoor settings, the pollutants can negatively influence cardiovascular, neurological, and respiratory health. Particulate matter (PM), which is a complex mixture of diverse particles (sulfate, ammonia, carbon, mineral dust, nitrate compounds), has been associated with morbidity and mortality related to respiratory and cardiovascular illness.[14,15] Sulfur dioxide and ozone both act as respiratory irritants and can trigger or deteriorate asthma and other respiratory conditions.[15,16] Nitrogen dioxide has also been associated with respiratory conditions such as asthma, bronchitis, increased susceptibility of lung infections, and wheezing.[15,17] Lead exists naturally or through the burning of fossil fuel, industries, and mining, and it is associated with neurological and renal problems amongst exposed individuals. Children are more vulnerable to the effects of lead.[2] It is evident from studies that air pollution has negative impacts on infants' and children's health and is linked with preterm birth, lung developmental/functional issues, and overall increased morbidity and mortality.[18–21] Since the lung tissue is still in development and over 80% of alveolar growth occurs after birth, infants are more susceptible to air pollution and environmental toxins.[22–24] In time-series studies conducted in cities with notoriously high levels of pollution, such as Mexico City, Seoul, and Sao Paulo, associations between particulate matter ≤10 μm (PM10) and infant mortality have been found.[25–27] Spatial similarities within the Czech Republic and the US have been reported between post-neonatal mortality and atmospheric particulate matter.[28,29]

HUMAN BEHAVIOR, MENTAL HEALTH, AND NEUROLOGICAL DISORDERS

The effect of noise, heat, and air pollution on human behavior, specifically aggression, has been documented. Although the respiratory and cardiovascular impacts of air pollution are well known, recent research shows that it also contributes to behavioral, psychological, and neurological issues. The mechanism of this is not precise. However, tiny pollution particles can reach the brain directly from nasal passages.[30,31] Furthermore, particles can also reach the brain after being absorbed in the blood through the alveoli.[31] Once these pollution particles reach the brain cells, they induce an inflammatory response that could lead to neurodegeneration.[31] The consequences of high and long-term exposure are seen in forms of cognitive decline, especially among children, causing hyperactivity, dementia, anxiety, depression, aggression, and can even predispose to Alzheimer's disease.[30,31] In one Chinese study, a high level of air pollution was associated with an increase in sedentary behavior, leading to other health issues.[32] In a UK-based study, reduced indoor and outdoor air quality significantly affected emotional and behavioral problems related to conduct/temper and hyperactivity among children.[33] Similar outcomes were noticed in a Californian study in which long-term exposure of PM2.5 possibly increased delinquent behavior among adolescents and teenagers.[34] Exposure to lead is known to cause harmful effects on the nervous tissue. Studies have shown that not

TABLE 1. Six criteria air pollutants

	Source	Characteristics	Health impacts (e.g. on organ systems)
Carbon Monoxide (CO)	outdoor (vehicles, burning fossil fuel), indoor air (gas heaters, stove, furnaces)	no odor, color, taste or irritation	cardiovascular, neurological, respiratory
Lead (Pb)	earth crust, burning fuel, mining, industries	bluish grey metal	neurological, renal, probable carcinogen
Nitrogen Oxides (NO & NO_2)	motor emission, burning of oil or coal, industries	non-flammable, colorless to brown	respiratory
Ozone (O_3)	motor emission, industries (boilers, chemicals)	main ingredient in smog	benefits: stratospheric ozone protects from UV radiation, harmful (ground level): respiratory
Sulfur Dioxide (SO_2)	coal and oil burning, volcanic eruptions	colorless, pungent	respiratory
Particulate Matter (PM)	chemical reactions between pollutants	mixture of solid and liquid particles, PM10: diameter ≤10 μm, PM2.5: diameter ≤2.5 μm (both PM10 and PM2.5 are inhalable)	respiratory, heart

only lead is associated with a decline in cognition, intellect, and memory among children and adolescents, but if exposure occurs at a young age and continuously, it can result in personality and behavioral issues in adulthood.[35,36] The literature also suggests lead exposure involvement in Parkinson's disease.[37] As per some research studies, smoking, which contributes to environmental air pollution, can increase the risk of Parkinson's, although other studies state the opposite.[37] Also, both active and passive smoking is linked with the etiology of multiple sclerosis.[38]

AIR POLLUTION AND COVID-19

As mentioned earlier, the long-term exposure to pollution has been connected to morbidity and mortality associated with respiratory inflammation, chronic lung disease, asthma, and cardiovascular disorders. A study examining data from over 3,000 US counties shows that in areas with slightly higher levels of PM2.5 (i.e., 1 μg/m^3), there was an 8% increase in COVID-19-related deaths.[39] Historically, this kind of relationship was also seen in a 2003 Chinese study where both short- and long-term exposure to air pollution was positively associated with severe acute respiratory syndrome (SARS)-related mortality.[40] Air pollution can also increase the incidence of COVID-19 as examined in a recent Chinese study where short-term exposure to O_3, PM (2.5 & 10), and NO_2 was significantly associated with higher numbers of COVID-19 cases.[41] Further studies are needed to explore the role of the PSI or air pollution indices, individual and combined effects of air pollutants on COVID-19 incidence, disease course, and mortality. Hypothesis testing based on the dose-response relationships, temporal trends, exposure inequality by geography, and monthly/yearly variation of air pollution on COVID-19 could provide crucial information about the dynamics and management of COVID-19 infection. More studies are needed to examine the interrelationship between the COVID-19 disease process and air pollutants. To examine this vital relationship, diverse and enhanced surveillance approaches coupled with multidisciplinary and mixed-method research studies can be crucial.[42,43]

SUMMARY & CONCLUSIONS

Environmental toxins and hazards have adverse impacts on humans throughout their lifespan. For instance, exposures during pregnancy can result in developmental issues, birth defects, intellectual delays, and cancers. After birth, while growing, they are more susceptible to air pollution and other toxins as their organs are still in developmental phases. Although all age groups are vulnerable to the effects of air pollution, the impacts are higher among people of extreme ages. The present short review examines the impact of air pollutants on humans and particularly explores associated mental health outcomes. The persistent exposure of pollutants can cause impairment of different organ systems. We also see that mortality is higher in places where air pollution is a significant issue. Furthermore, early studies are showing unfavorable COVID-19-related outcomes in the presence of high levels of air pollutants. More research is needed to examine the interrelationship between the COVID-19 disease process and air pollutants, with the use of multidisciplinary research studies. Rapid industrialization, increased use of cars, buses, and airplanes during the last

and current centuries have contributed to public health issues related to air pollution. It is known that the use of motor vehicles can contribute largely to the pollution in a geographical area; hence, changes in transportation mode (e.g., reduced use of cars, increased use of bicycles, electric vehicles, or mass public transportation etc.) can help in reducing this problem. City planning, opportunities to provide easy access to the public transportation systems, increase in vegetation, and plantation of trees can also contribute.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. National Institute of Environmental Health Sciences. Air Pollution and Your Health. https://www.niehs.nih.gov/health/topics/agents/air-pollution/index.cfm
2. World Health Organization. Air pollution.https://www.who.int/health-topics/air-pollution#tab=tab_1
3. Bobak M, Leon DA. The effect of air pollution on infant mortality appears specific for respiratory causes in the postneonatal period. *Epidemiology*. 1999;10:666-70.
4. Hajat S, Armstrong B, Wilkinson P, Busby A, Dolk H. Outdoor air pollution and infant mortality: analysis of daily time-series data in 10 English cities. *Journal of Epidemiology & Community Health*. 2007;61:719-722.
5. Centers for Disease Control and Prevention. Air Quality, Air Pollutants. https://www.cdc.gov/air/pollutants.htm
6. United States Environmental Protection Agency. Carbon Monoxide (CO) Pollution in Outdoor Air. https://www.epa.gov/co-pollution/basic-information-about-carbon-monoxide-co-outdoor-air-pollution#What%20is%20CO
7. United States Environmental Protection Agency. Ground-level Ozone Pollution. https://www.epa.gov/ground-level-ozone-pollution
8. United States Environmental Protection Agency. Particulate Matter (PM) Pollution. https://www.epa.gov/pm-pollution/particulate-matter-pm-basics#PM
9. U. S. Environmental Protection Agency. Pollutant Standard Index (PSI). https://www3.epa.gov/ttnamti1/archive/psi.html
10. United States Environmental Protection Agency. Indoor Air Quality (IAQ). https://www.epa.gov/indoor-air-quality-iaq/introduction-indoor-air-quality
11. Akram H, Ashraf G. Commentary: Second-hand smoke and other potential lung cancer exposures among non-smoking women. *International Journal of Medical Sciences and Technology*. 2017;7:25.
12. Kim C, Gao YT, Xiang YB, et al. Home kitchen ventilation, cooking fuels, and lung cancer risk in a prospective cohort of never smoking women in Shanghai, China. *Int J Cancer*. 2015;136:632-638.
13. Ko YC, Lee CH, Chen MJ, et al. Risk factors for primary lung cancer among non-smoking women in Taiwan. *Int J Epidemiol*. 1997;26:24-31.
14. World Health Organization. Ambient (outdoor) air pollution. https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health
15. Davidson CI, Phalen RF, Solomon PA. Airborne particulate matter and human health: a review. *Aerosol Science and Technology*. 2005;39:737-749.
16. EPA. Indoor Air Quality (IAQ). Ozone Generators that are Sold as Air Cleaners. https://www.epa.gov/indoor-air-quality-iaq/ozone-generators-are-sold-air-cleaners#:~:text=When%20inhaled%2C%20ozone%20can%20damage,body%20to%20fight%20respiratory%20infections
17. Nitschke M. Respiratory health effects of nitrogen dioxide exposure and current guidelines. *International Journal of Environmental Health Research*. 1999;9:39-53.
18. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Health effects of outdoor air pollution. *Am J Respir Crit Care Med*. 1996;153:3-50.
19. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Health effects of outdoor air pollution. Part 2. *Am J Respir Crit Care Med*. 1996;153:477-498.
20. Kim JJ. Ambient air pollution: health hazards to children. *Pediatrics*. 2004;114:1699-1707.
21. Schwartz J. Air pollution and children's health. *Pediatrics*. 2004;113:1037-1043.
22. Dietert RR, Etzel RA, Chen D, et al. Workshop to identify critical windows of exposure for children's health: immune and respiratory systems work group summary. *Environ Health Perspect*. 2000;108:483-490.
23. Plopper CG, Fanucchi MV. Do urban environmental pollutants exacerbate childhood lung diseases? *Environ Health Perspect*. 2000;108:A252-A253.
24. Pinkerton KE, Joad JP. The mammalian respiratory system and critical windows of exposure for children's health. *Environmental Health Perspectives*. 2000;108:457-462.
25. Loomis D, Castillejos M, Gold DR, McDonnell W, Borja-Aburto VH. Air pollution and infant mortality in Mexico City. *Epidemiology*. 1999:118-123.
26. Ha EH, Lee JT, Kim H, et al. Infant susceptibility of mortality to air pollution in Seoul, South Korea. *Pediatrics*. 2003;111:284-290.
27. Lin CA, Pereira LA, Nishioka DC, Conceição GM, Braga AL, Saldiva PH. Air pollution and neonatal deaths in Sao Paulo, Brazil. *Brazilian Journal of Medical and Biological Research*. 2004;37:765-770.
28. Bobak M, Leon DA. Air pollution and infant mortality in the Czech Republic, 1986-88. *The Lancet*. 1992;340:1010-1014.
29. Woodruff TJ, Grillo J, Schoendorf KC. The relationship between selected causes of postneonatal infant mortality and particulate air pollution in the United States. *Environmental Health Perspectives*. 1997;105:608-612.
30. Peeples L. News Feature: How air pollution threatens brain health. *Proceedings of the National Academy of Sciences*. 2020;17:13856-13860
31. Weir K. Smog in our brains. *Monitor on Psychology*. 2012;43:32.
32. Yu H, Cheng J, Gordon SP, et al. Impact of Air Pollution on Sedentary Behavior: A Cohort Study of Freshmen at a University in Beijing, China. *Int J Environ Res Public Health*. 2018;15:2811.
33. Midouhas E, Kokosi T, Flouri E. The quality of air outside and inside the home: associations with emotional and behavioural problem scores in early childhood. *BMC Public Health*. 2019;19:406.
34. Younan D, Tuvblad C, Franklin M, et al. Longitudinal analysis of particulate air pollutants and adolescent delinquent behavior in Southern California. *Journal of Abnormal Child Psychology*. 2018;46:1283-1293.
35. Williams JH, Ross L. Consequences of prenatal toxin exposure for mental health in children and adolescents. *European Child & Adolescent Psychiatry*. 2007;16:243-253.
36. Reuben A, Schaefer JD, Moffitt TE, et al. Association of Childhood Lead Exposure With Adult Personality Traits and Lifelong Mental Health. *JAMA Psychiatry*. 2019;76:418-425.
37. Elbaz A, Moisan F. Update in the epidemiology of Parkinson's disease. *Current Opinion in Neurology*. 2008;21:454-460.
38. Lauer K. Environmental risk factors in multiple sclerosis. *Expert Review of Neurotherapeutics*. 2010;10:421-440.
39. Wu X, Nethery RC, Sabath BM, Braun D, Dominici F. Exposure to air pollution and COVID-19 mortality in the United States. *medRxiv*. 2020 Jan 1.
40. Cui Y, Zhang ZF, Froines J, et al. Air pollution and case fatality of SARS in the People's Republic of China: an ecologic study. *Environmental Health*. 2003;2:1-5.
41. Zhu Y, Xie J, Huang F, Cao L. Association between short-term exposure to air pollution and COVID-19 infection: Evidence from China. *Sci Total Environ*. 2020;727:138704.
42. Aslam F, Akram H. Mixed-Methodology in Disease Surveillance, Response, and Control. *Int J Basic Sci Med*. 2019;2:43-44.
43. Akram H. Enhancing Public Health Capacity by using Epidemiological Teams in a Public Health Setting. *Cureus*. 2017;9:e1381.

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Journal of Interdisciplinary Medicine

ORIGINAL RESEARCH

PHYSICAL MEDICINE AND REHABILITATION // CARDIOLOGY

Is Physical Therapy the Early Solution for Post-Acute Myocardial Infarction Patients? A Meta-Analysis

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ABSTRACT

Background: Physical rehabilitation is essential to improve the quality of life of patients with acute myocardial infarction (AMI). **Study aim:** The study intended to demonstrate the benefits of early rehabilitation in patients with AMI. **Material and method:** We performed a meta-analysis to document the benefits of physical treatment in patients who suffered an AMI. Studies were searched in the following databases: PubMed, PlosOne, Mendeley, and clinicaltrials.gov. The terms used in our research were “rehabilitation”, “physical exercise”, “physical training” “quality of life”, “early”, and “post MI”. The inclusion criteria consisted in the assessment of the following parameters: heart rate, maximal/submaximal capacity, and characteristics of the left ventricle – end-diastolic volume, ejection fraction, and left ventricle hypertrophy included in the study design. **Results:** The database search identified 710 studies, of which only 10 passed the inclusion criteria. Out of 1,515 patients who underwent early physical therapy, 960 reported improvement in the quality of their life ($p < 0.001$). A number of 2,703 patients out of a total of 3,595 underwent a complete physical treatment and medication program. From the ten studies included in the meta-analysis, six had a positive feedback to the multimodal treatment within 1 month post-AMI. Patients who performed physical exercises within a month after the cardiac arrest (1,103 post-AMI patients from a total of 1,278) demonstrated a high heterogeneity represented by the coefficient $I2 = 84\%$ but with a significant statistical value of $p < 0.00001$. **Conclusion:** Early physical therapy initiation significantly improves the quality of life of patients with AMI.

Keywords: physical therapy, myocardial infarction, early exercise

INTRODUCTION

The quality of life of patients suffering from an acute myocardial infarction (AMI) depends of several variables. The main consequence of AMI is left ventricular remodeling, and several studies have shown its improvement in patients who benefited from physical treatment following an acute myocardial infarction.

PURPOSE

The purpose of this study was to demonstrate the benefits of early rehabilitation in patients with AMI.

MATERIAL AND METHODS

We performed a meta-analysis to document the benefits of physical treatment in patients who suffered an AMI. The terms used in our research were "rehabilitation", "physical exercise", "physical training" "quality of life", "early", and "post MI". The inclusion criteria consisted in the assessment of the following parameters: heart rate, maximal/submaximal capacity, and characteristics of the left ventricle – end-diastolic volume, ejection fraction, and left ventricle hypertrophy in the design of the study.[1–4] Statistical analysis was performed using RevMan 5.4 software.

RESULTS

The database search identified 710 studies, of which only 10 passed the inclusion criteria, including a number of 1,061 patients out of a total of 1,546 who participated in a complete physical treatment and medication program.

The first question was whether the life of patients with myocardial infarction had improved after early initiation of kinesiotherapy. A number of 2,475 patients out of 3,526 who underwent early physical therapy reported improvement in the quality of their life (Figure 1). Improvement in the quality of life has been defined as improvement of the following conditions: fatigue, depression, daily activities. The answers to the first question are summarized in Table 1.

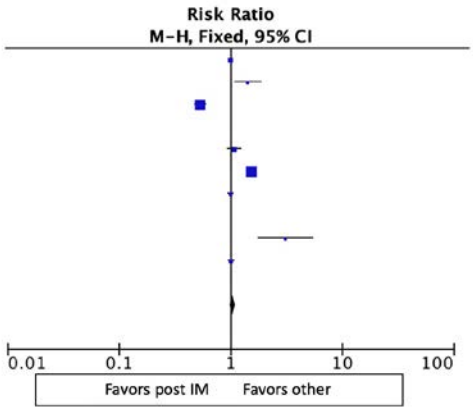

FIGURE 1. Forest plot diagram of the studies with patients whose quality of life has improved after post-MI rehabilitation

The Cochrane-Q number (df = 7) was 265.68, with I^2 expressing a 97% heterogeneity ($p < 0.07$, $Z = 1.79$). I^2 represents study heterogeneity as studies with different designs that can induce biased data. All patients who underwent a complete physical training exhibited an improvement in their quality of life, demonstrating that early initiation of physical exercise has a positive impact on quality of life in the post-infarction period.

The next hypothesis we have intended to verify was related to the effectiveness of the physical rehabilitation program after one month in patients that had presented with myocardial infarction.

TABLE 1. Effect of initiation of rehabilitation measures post AMI

Study or Subgroup	Experimental		Control		Weight	Odds Ratio
	Events	Total	Events	Total		
Soleimani *et al.*[5] (2008)	178	178	62	62	10.0%	1.00 [0.98, 1.02]
Kim et al.[6] (2014)	18	18	18	26	1.7%	1.42 [1.09, 1.85]
Hansen et al.[7] (2008)	170	334	330	343	35.2%	0.53 [0.48, 0.59]
Giallauria et al.[8] (2006)	15	15	0	0		Not estimable
Chen et al.[9] (2015)	50	64	561	770	9.3%	1.07 [0.94, 1.23]
Larsen et al.[10] (2011)	382	528	430	908	34.2%	1.53 [1.40, 1.67]
Kargarfard et al.[11] (2010)	35	35	37	37	3.9%	1.00 [0.95, 1.05]
Andjic et al.[12] (2016)	60	60	0	0		Not estimable
Izeli et al.[13] (2016)	18	18	8	26	0.8%	3.09 [1.76, 5.42]
Sumide et al.[14] (2009)	34	34	69	70	5.0%	1.01 [0.96, 1.06]
Total (95% CI)	**1,284**		**2,272**		**100%**	**1.04 [1.00, 1.10]**
Total events	960		1,515			

Heterogeneity: $Chi^2 = 265.68$, df = 7 ($p < 0.0001$); $I^2 = 97\%$
Test for overall effect: $Z = 1.79$ ($p = 0.07$)

TABLE 2. Effectiveness of the rehabilitation program within one month post AMI

Study or Subgroup	Experimental		Control		Weight	Odds Ratio
	Events	Total	Events	Total		
Soleimani *et al.*[5] (2008)	178	178	62	62		Not estimable
Kim et al.[6] (2014)	18	18	18	26	0.2%	17.00 [0.91, 316.49]
Hansen et al.[7] (2008)	272	334	339	343	31.4%	0.05 [0.02, 0.14]
Giallauria et al.[8] (2006)	15	15	13	15	0.2%	5.74 [0.25, 130.37]
Chen et al.[9] (2015)	50	64	561	834	8.8%	1.74 [0.94, 3.20]
Larsen et al.[10] (2011)	382	528	380	430	58.6%	0.34 [0.24, 0.49]
Kargarfard et al.[11] (2010)	35	35	37	37		Not estimable
Andjic et al.[12] (2016)	60	60	60	60		Not estimable
Izeli et al.[13] (2016)	18	18	8	26	0.1%	80.53 [4.33, 1499.20]
Sumide et al.[14] (2009)	33	34	69	70	0.7%	0.48 [0.03,7.89]
Total (95% CI)	**1,284**		**1,903**		**100%**	**0.50 [0.39, 0.63]**
Total events	1,061		1,547			

Heterogeneity: Chi² = 58.73, df = 6 (p <0.00001); I² = 90%
Test for overall effect: Z = 5.75 (p <0.00001)

From the 10 studies analyzed, 7 studies had a positive feedback regarding the multimodal treatment within one month post myocardial infarction (Table 2).

This analysis presented a high heterogeneity (I^2 = 90%, p <0.00001). In this regard, the most appropriate study design was the one published by Chen *et al.* in 2015 (Figure 2). This study included 60 patients with AMI, of which 50 participated in a physical exercise program within one month after the cardiac event.[9] The studies that had crossed the "no effect" line were not statistically significant for our meta-analysis (Figure 2).

The next hypothesis was whether kinesiotherapy has been beneficial for post-AMI patients. Out of the 10 studies, six had statistical significance for our meta-analysis, with a p value <0.00001 (Table 3, Figure 3).

In a study by Chen *et al.* (2015), beneficial changes have been noticed after kinesiotherapy in 610 out of 834 patients.[9]

Even though the heterogeneity of the studies was low compared with the outcomes of other studies, only the studies of Chen *et al.*[9] and Izeli *et al.*[13] did not cross the "no effect" line, therefore being statistically significant for our meta-analysis. However, the study of Izeli *et al.* had to be dismissed due to its inappropriate design and limitations (Figure 3).[13]

The question whether the implementation of an exercise program within one week at most after the cardiac event would be beneficial for post-AMI patients could not be elucidated because there were no relevant data identified in the medical literature.

The last hypothesis addresed in this meta-analysis was related to the rehabilitation program, whether this should be initiated early or within one month after the cardiac event. The following data were obtained: the limits of the confidence interval between 2.04 and 3.09

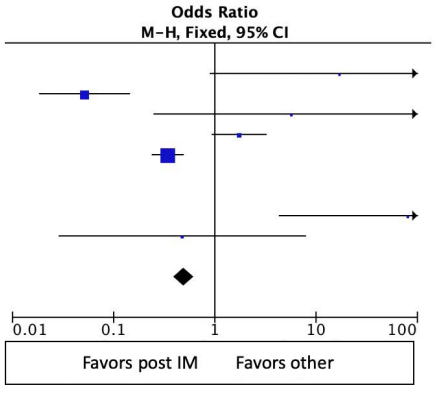

FIGURE 2. Forest plot diagram of the studies with patients who underwent a rehabilitation program within one month post MI

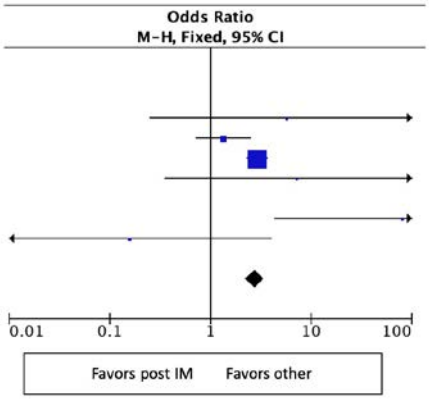

FIGURE 3. Forest plot diagram of the studies with patients who benefited from kinesiotherapy post MI

TABLE 3. Effect of kinesiotherapy post AMI

Study or Subgroup	Experimental		Control		Weight	Odds Ratio
	Events	Total	Events	Total		
Soleimani *et al*.[5] (2008)	62	62	178	178		Not estimable
Kim et al.[6] (2014)	18	18	26	26		Not estimable
Hansen et al.[7] (2008)	334	334	343	343		Not estimable
Giallauria et al.[8] (2006)	15	15	13	15	0.5%	5.74 [0.25, 130.37]
Chen et al.[9] (2015)	50	64	56	770	2.0%	45.54 [23.72, 87.41]
Larsen et al.[10] (2011)	382	548	430	908	94.6%	2.91 [2.31, 3.66]
Kargarfard et al.[11] (2010)	35	25	34	37	0.5%	7.20 [0.36, 144.67]
Andjic et al.[12] (2016)	60	60	60	60		Not estimable
Izeli et al.[13] (2016)	18	18	8	26	0.2%	80.53 [4.33, 1499.20]
Sumide et al.[14] (2009)	33	34	70	70	2.2%	0.16 [0.01, 3.99]
Total (95% CI)	**1,168**		**2,433**		**100%**	**3.91 [3.17, 4.81]**
Total events	1,007		1,218			

Heterogeneity: Chi² = 68.88, df = 5 (p <0.00001); I² = 93%
Test for overall effect: Z = 12.80 (p <0.00001)

with a Z value of 8.73, and a statistical significance of p <0.00001, favoring the early initiation of the rehabilitation program in post-AMI patients. Nevertheless, study heterogeneity was still high, with I^2 = 84%. According to the forest diagram, the study with the narrowest confidence interval was the one conducted by Kim *et al*. in 2014, which still crossed the "no effect" line.[6] This study included 18 patients, of which 8 responded better to the early initiation of the kinesiotherapy program (Figure 4).

Five out of 10 studies did not have sufficient weight to be considered relevant in this analysis. The only study that did not cross the „no effect" line was the one conducted by Chen *et al*. in 2015, in which that the majority of patients (50 out of 64) benefited from early rehabilitation.[9]

DISCUSSIONS

The present study on the quality of life of post-AMI patients who underwent physical rehabilitation has identified that physical therapy might be the early solution for post-AMI subjects.

The study aimed to address five questions regarding post-AMI patients: 1) whether their quality life has improved after early initiation of kinesiotherapy; 2) wheth-

TABLE 4. Effect of early kinesiotherapy post MI

Study or Subgroup	Experimental		Control		Weight	Odds Ratio
	Events	Total	Events	Total		
Soleimani *et al*.[5] (2008)	172	172	62	62		Not estimable
Kim et al.[6] (2014)	8	18	18	26	6.9%	0.36 [0.10, 1.24]
Hansen et al.[7] (2008)	334	334	343	343		Not estimable
Giallauria et al.[8] (2006)	15	15	15	15		Not estimable
Chen et al.[9] (2015)	50	64	560	770	15.8%	1.34 [0.73, 2.47]
Larsen et al.[10] (2011)	382	528	430	908	73.3%	2.91 [2.31, 3.66]
Kargarfard et al.[11] (2010)	30	35	34	37	4.0%	0.53 [0.12, 2.40]
Andjic et al.[12] (2016)	60	60	60	60		Not estimable
Izeli et al.[13] (2016)	18	18	8	26	0.2%	80.53 [4.33, 1499.20]
Sumide et al.[14] (2009)	34	34	70	70		Not estimable
Total (95% CI)	**1,278**		**2,317**		**100%**	**2.51 [2.04, 3.09]**
Total events	1,103		1,600			

Heterogeneity: Chi² = 24.489, df = 4 (p <0.0001); I² = 84%
Test for overall effect: Z = 8.73 (p <0.00001)

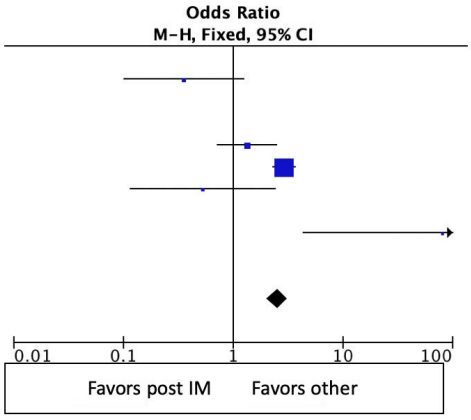

FIGURE 4. Forest plot diagram of the studies with patients who benefited from early kinesiotherapy post MI

er the physical rehabilitation program is efficient at one month post AMI; 3) whether kinesiotherapy has beneficial effects; 4) whether the implementation of an exercise program within one week at most after the cardiac event would be beneficial; and 5) whether the rehabilitation program should be started early or within a month from the acute cardiac event.

Our results have shown that early initiation of physical therapy may improve the quality of life of patients with AMI. Similarly to our results, a report by Haykowsky *et al*. published in 2015 found that kinesiotherapy is beneficial in the post-AMI phase, and a kinesiotherapy program initiated early could improve the rehabilitation of these patients.[15] A meta-analysis published by Taylor *et al*. in 2004, which included 48 trials on a total of 8,940 patients, confirmed the benefits of cardiac rehabilitation for patients with coronary heart disease.[16] Also, in 2019, Ji *et al*. published a meta-analysis which demonstrated that cardiac rehabilitation reduces the recurrence of myocardial infarction.[17]

CONCLUSIONS

In conclusion, early initiation of physical therapy may improve the quality of life of patients with AMI and may reduce ventricular remodeling. Kinesiotherapy within one month from the index event may have a significant beneficial role in patients with cardiovascular diseases, especially following an AMI. An early initiated kinesiotherapy program could improve the rehabilitation of post-AMI patients. However, there is limited data on the benefits of urgent initiation of a physical rehabilitation program, within one week after the event, therefore this hypothesis should be further analyzed in larger scale studies.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
2. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
3. Petrie A, Bulman JS, Osborn JF. Further statistics in dentistry Part 8: Systematic reviews and meta-analyses. *Br Dent J*. 2003;194:73-78.
4. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol*. 2001;54:1046-1055.
5. Soleimani A, Alidoosti M, Salarifar M, Kassaian SE, Karimi A, Davoodi S, et al. Effect of Cardiac Rehabilitation Program on Heart Rate Recovery after Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting. *J Tehran Univ Heart Cent*. 2008;3:11-16.
6. Kim C, Jung H, Choi HE, Kang SH. Cardiac Rehabilitation After Acute Myocardial Infarction Resuscitated From Cardiac Arrest. *Ann Rehabil Med*. 2014;38:799-804.
7. Hansen D, Dendale P, Berger J, Onkelinx S, Reyckers I, Hermans A, et al. Importance of exercise training session duration in the rehabilitation of coronary artery disease patients. *Eur J Cardiovasc Prev Rehabil Off J Eur Soc Cardiol Work Groups Epidemiol Prev Card Rehabil Exerc Physiol*. 2008;15:453-459.
8. Giallauria F, De Lorenzo A, Pilerci F, Manakos A, Lucci R, Psaroudaki M, et al. Long-term effects of cardiac rehabilitation on end-exercise heart rate recovery after myocardial infarction. *Eur J Cardiovasc Prev Rehabil Off J Eur Soc Cardiol Work Groups Epidemiol Prev Card Rehabil Exerc Physiol*. 2006;13:544-550.
9. Chen H-M, Liu C-K, Chen H-W, Shia B-C, Chen M, Chung C-H. Efficiency of rehabilitation after acute myocardial infarction. *Kaohsiung J Med Sci*. 2015;31:351-357.
10. Larsen KK, Vestergaard M, Søndergaard J, Christensen B. Rehabilitation status three months after first-time myocardial infarction. *Scand J Prim Health Care*. 2011;29:210-215.
11. Kargarfard M, Rouzbehani R, Basati F. Effects of Exercise Rehabilitation on Blood Pressure of Patients after Myocardial Infarction. *Int J Prev Med*. 2010;1:124-130.
12. Andjic M, Spiroski D, Ilic Stojanovic O, Vidakovic T, Lazovic M, Babic D, et al. Effect of short-term exercise training in patients following acute myocardial infarction treated with primary percutaneous coronary intervention. *Eur J Phys Rehabil Med*. 2016;52:364-369.
13. Izeli NL, dos Santos AJ, Crescêncio JC, Gonçalves ACCR, Papa V, Marques F, et al. Aerobic Training after Myocardial Infarction: Remodeling Evaluated by Cardiac Magnetic Resonance. *Arq Bras Cardiol*. 2016;106:311-318.
14. Sumide T, Shimada K, Ohmura H, Onishi T, Kawakami K, Masaki Y, et al. Relationship between exercise tolerance and muscle strength following cardiac rehabilitation: comparison of patients after cardiac surgery and patients with myocardial infarction. *J Cardiol*. 2009;54:273-281.
15. Haykowsky M, Scott J, Esch B, Schopflocher D, Myers J, Paterson I, et al. A meta-analysis of the effects of exercise training on left ventricular remodeling following myocardial infarction: start early and go longer for greatest exercise benefits on remodeling. *Trials*. 2011;12:92.
16. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med*. 2004;116:682-692.
17. Ji H, Fang L, Yuan L, Zhang Q. Effects of Exercise-Based Cardiac Rehabilitation in Patients with Acute Coronary Syndrome: A Meta-Analysis. *Med Sci Monit Int Med J Exp Clin Res*. 2019;25:5015-5027.

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ORIGINAL RESEARCH

OBSTETRICS AND GYNECOLOGY // NEONATOLOGY

The Influence of Oxidative Stress-Related Factors on Pregnancy and Neonatal Outcomes

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ABSTRACT

Background: Pregnancy is a physiological process associated with an excessive oxidative stress for both the mother and the neonate. Oxidative stress was extensively studied and is still in focus as a factor of maternal pathologies during pregnancy, with consequences on the outcome of the neonate. **Aim:** The aim of our study was to determine whether oxidative stress-related factors can influence the outcome of pregnancy, delivery, and the neonate's wellbeing. **Material and methods:** The study was conducted using a questionnaire among pregnant women with voluntary enrollment. Exclusion criteria were preeclampsia or other cardiovascular diseases, gestational diabetes, and hypothyroidism at admission. Patients were enrolled in a control group of 60 pregnant women without preexisting pathology and pregnancy with physiological course, a premature group of 21 pregnant women with premature delivery, and a cardiac group of 8 pregnant women with fetal heart disease known before birth. The study population was separated into subgroups based on dietary supplement use within the three main groups, and other subgroups for smoking/non-smoking mothers in the control group and one for smoking/non-smoking mothers in the premature and cardiac groups together. **Results:** The mean Apgar score at 1 minute was significantly higher in the control group compared to the cardiac group ($p = 0.0023$). The 1-minute Apgar score was significantly lower in infants that were born premature, from smoking mothers, compared to babies that were delivered at term ($p = 0.0191$). Although we did not obtain significant differences in birth weight corrected by gestational age between the control (mature) group and premature group, there was a good correlation in gestational age and birth weight of the preterm born infants ($r = 0.8517$, $p < 0.0001$). **Conclusions:** Smoking can aggravate oxidative stress in pregnancy, which will contribute to a difficult postnatal adaptation of newborns from smoking mothers and will increase the risk of premature delivery.

Keywords: pregnancy, smoking, Apgar score, oxidative stress, neonate

INTRODUCTION

Oxidative stress is the imbalance between the prooxidant mechanisms (protein, membrane, and DNA oxidation) and antioxidant defenses of the body. It is caused by excess of reactive oxygen, nitrogen, and chlorine species and reactive intermediates, which are causing cell, tissue, and DNA damage. This aggression can be counteracted by enzymatic or non-enzymatic antioxidants in normal, healthy pregnancy, physiological labor, and delivery without any complications.

However, with the disturbance of the defense system, an intensive oxidative aggression occurs, which can be the precursor for multiple complications in pregnant women: eclampsia, miscarriage, preterm labor, and intrauterine growth retardation. In case of fetal involvement, this aggression may lead to perinatal diseases: bronchopulmonary dysplasia/chronic lung disease, necrotizing enterocolitis, and retinopathy of prematurity, called by Saugstad the "oxygen radical diseases of neonatology". Later, the list was completed with periventricular leukomalacia.[1,2]

The placenta has been proven to be the major source of oxidative stress during pregnancy as it is rich in lipid peroxides. The oxidative stress effect is under the control of the placental antioxidant enzymes.[3] Furthermore, both labor and delivery are accompanied by an increase of oxidative stress markers and simultaneously by a decrease in antioxidant capacity. A study conducted by Arguelles *et al.* on circulating oxidative stress biomarkers in maternal and umbilical cord blood concluded that a higher oxidative state in the maternal blood correlates with a higher oxidative state in the umbilical cord blood.[4] Oxidative stress during embryogenesis and fetal development has an influence on the metabolism of the fetus via gene expression and/or lipid and protein peroxidation.[5,6]

The antioxidant activity should balance the high production of free radicals in normal, uncomplicated pregnancy. However, the concentration of the components of the antioxidant defense system might not be sufficient to counteract the effects of oxidative stress.[6] The antioxidants that protect the body against oxidative stress can be grouped into endogenous (enzymatic, non-enzymatic) and exogenous (natural, synthetic) antioxidants.[7]

Environmental factors and maternal diet can have an influence on the increased oxidative stress or decreased antioxidant status during pregnancy. Turpeinen *et al.* and Maziere C *et al.* showed in their studies that a diet rich in polyunsaturated acids could contribute to oxidative stress associated with preeclampsia. Burke noted that a deficient diet was related with greater risk of preeclampsia. Clausen *et al.* confirmed that the occurrence of preeclampsia tends to rise with increasing calorie intake and polyunsaturated fats in the diet.[8–12]

A study conducted by Arguelles *et al.* showed a higher risk of increased oxidative stress and its aggression on lipids and proteins in smoking mothers compared with non-smoking ones, and the decrease of antioxidant capacity related to smoking.[4] Maternal smoking during pregnancy increases the risk of complications such as stillbirth, premature delivery, lower birth weight, altered cardio-respiratory response, cleft palate, and sudden infant death syndrome, as well as long-term neurobehavioral effects.[13–16]

MATERIAL AND METHODS

Our study was conducted using a questionnaire completed by pregnant women admitted to the Obstetrics-Gynecology Clinic I of the Emergency Clinical County Hospital of Târgu Mureș between November 2019 and October 2020. The study has been approved by the Ethics Committee of the hospital and of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, and participation of the included patients was voluntary. In each case, written informed consent was obtained from the participants.

The questionnaire inquired about personal information (name, age, address, phone number), biometric parameters (height, weight, blood pressure, parity, delivery data), lifestyle data (fruit and vegetable consumption, soft drinks, non-alcoholic drinks, coffee, tea, alcohol, smoking habits, dietary supplements, habitual stress, sports), health-related information (preexisting pathology, infectious diseases, pharmaceutical treatment). Exclusion criteria were preeclampsia or other cardiovascular diseases, gestational diabetes, and hypothyroidism at admission. Data was recorded at admission by highly qualified and trained hospital personnel, during labor. Information about the delivery and the newborn were obtained after delivery from the patients' medical records (delivery type, birth weight, 1- and 5-minute Apgar score).

The participants were categorized into three groups: the *control* group included 60 pregnant women with no preexisting pathology and physiological pregnancy; the *premature* group included 21 pregnant women with premature rupture of membrane and risk for premature delivery; and the *cardiac* group included 8 pregnant women with known fetal cardiac disease. The study population was further separated into subgroups based on smoking/non-smoking status for the control group and for the premature and cardiac groups together. In this group, the ex-

TABLE 1. Baseline characteristics of the study groups

Characteristics	Control group (n = 60)	Premature group (n = 21)	Cardiac group (n = 8)
Parity			
Primiparity	30 (50%)	8 (38.09%)	4 (50%)
Multiparity	30 (50%)	13 (61.90%	4 (50%)
Delivery mode	9 (75)	7 (6.48)	0.0001
Vaginal	51 (85%)	14 (66.67%)	3 (37.50%)
Caesarian	9 (15%)	7 (33.33 %)	5 (62.50%)

clusion criterion was non-responding to the question on smoking habits. Another subgroup was created based on dietary supplement use within the three main groups.

Our study complied with the Declaration of Helsinki. Statistical analysis was performed with GraphPad InStat version 3 (GraphPad Software Inc, California, USA). We used Student's unpaired t test, with and without Welch correction, Pearson's correlation test, and Fischer's test. The level of significance was set to $p < 0.05$.

RESULTS

The average age of the mothers from the three groups did not show significant differences. Data regarding baseline characteristics, including parity and delivery mode, are shown in Table 1, while maternal ages, gestational ages, birth weights, and Apgar scores at 1 and 5 minutes are shown in Table 2.

The weight at birth was not significantly different between the control and cardiac groups, and neither between the subgroups of premature babies from smoking and non-smoking mothers.

Premature newborns had a quasi-harmonious intrauterine growth; there were no differences in weight gain adjusted to gestational age, as there was a statistically significant correlation between the two parameters ($r = 0.8517$, $p < 0.0001$), as shown in Figure 1.

Regarding the habitual use of dietary supplements there were no statistically significant differences in the mean birth weight between the subgroups of either the control or the premature group.

Postnatal adaptation was assessed by the Apgar score at 1 minute and 5 minutes of life. We obtained statistically significant differences in 1-minute Apgar scores between the control and cardiac groups with 9.08 ± 1.61 versus 7.87 ± 1.24 points, respectively ($p = 0.02$) (Figure 2).

The same statistically significant differences were observed in case of the 5-minute Apgar score, with a mean value of 9.45 ± 1.39 versus 8 ± 0.92 points, respectively ($p = 0.005$).

TABLE 2. Maternal and neonatal clinical characteristics

Characteristics	Control group (n = 60)	Premature group (n = 21)	p value
Maternal age (years, mean ± SD)	26.47 ± 6.24	23.33 ± 6.72	0.93
Gestational age (weeks, mean ± SD)	38.93 ± 0.95	32.00 ± 3.91	<0.0001*
Birth weight (g, mean ± SD)	3,409.66 ± 411.22	1,905 ± 784.73	<0.0001*
Apgar score at 1 minute	9.08 ± 1.62	7.95 ± 1.84	0.01*
Apgar score at 5 minutes	9.45 ± 1.40	8.86 ± 0.91	0.07
Characteristics	**Control group (n = 60)**	**Cardiac group (n = 8)**	**p value**
Maternal age (years, mean ± SD)	26.47 ± 6.24	28.88 ± 5.67	0.30
Gestational age (weeks, mean ± SD)	38.93 ± 0.95	39.00 ± 0.93	0.72
Birth weight (g, mean ± SD)	3,409.66 ± 411.22	3,328.57 ± 850.03	0.8
Apgar score at 1 minute	9.08 ± 1.62	7.95 ± 1.84	0.05
Apgar score at 5 minutes	9.45 ± 1.40	8.00 ± 0.93	0.005

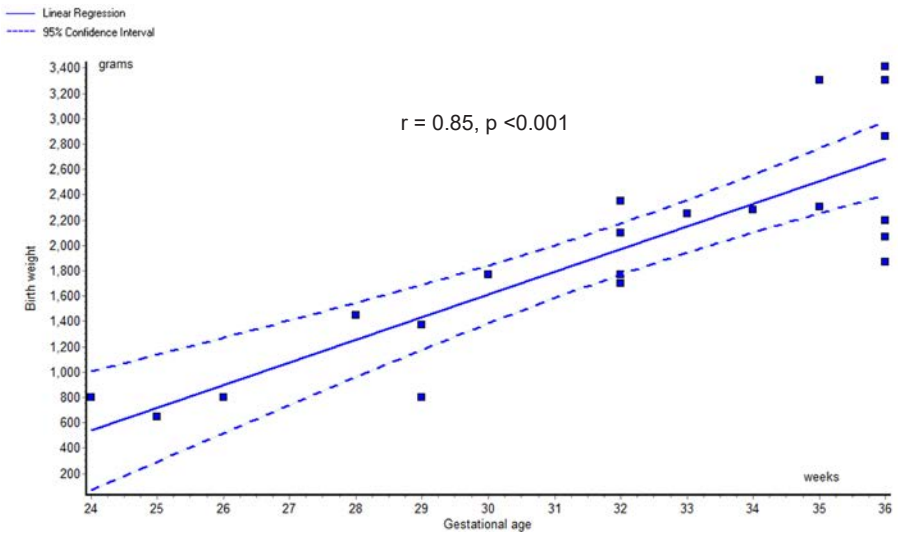

FIGURE 1. Correlation between gestational age and birth weight in the premature group

There were no statistically significant differences in mean values of the 5-minute Apgar score between the control (mature) and the premature groups (p = 0.07). As expected, the premature infants presented a significantly lower Apgar score at 1 minute compared to controls (7.95 ± 1.83 versus 9.08 ± 1.61, p = 0.01 (Table 2).

While assessing the newborns' postnatal outcomes in presence of maternal smoking, we observed that smoking influenced the Apgar score at 1 and 5 minutes in the two subgroups of preterm infants (smoking vs. non-smoking: 7.10 ± 2.07 vs. 8.72 ± 1.19, p = 0.01 at 1 minute, and 8.4 ± 0.84 vs. 9.27 ± 0.78 points, p = 0.02 at 5 minutes) (Figure 3).

This statistically significant difference was not observed in case of the control versus cardiac groups divided in subgroups according to smoking habits. The incidence of maternal smoking in the control group was significantly lower than in the premature + cardiac pooled groups. Maternal smoking was significantly more frequent in case of infants who were premature or born with cardiac congenital anomalies compared to controls (p = 0.035, RR = 2.29), as shown in Figure 4.

Lifestyle- and health-related parameters, including the presence of smoking, dietary supplements, everyday stress, and maternal pathology are presented in Table 3.

Maternal pathology at admission included anemia, gestational edema, myopia, thrombophilia, thrombocytopenia, lupus erythematosus, obesity, respiratory viral infection. In the premature group, preeclampsia was present in one case and non-obstructive hypertrophic cardiomyopathy in one case.

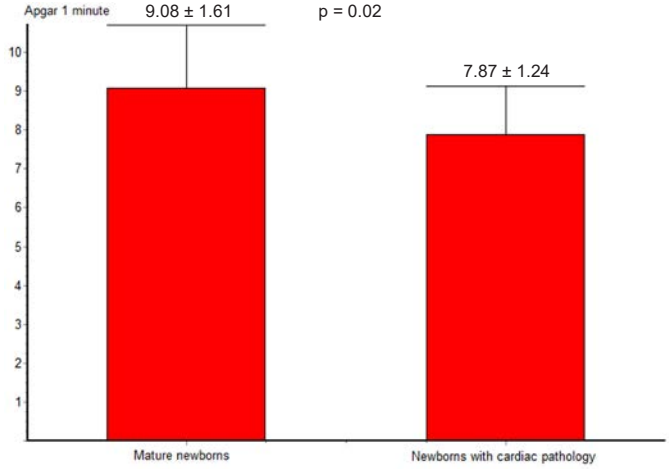

FIGURE 2. The Apgar score at 1 minute in the newborns of the control (mature) group versus the cardiac group

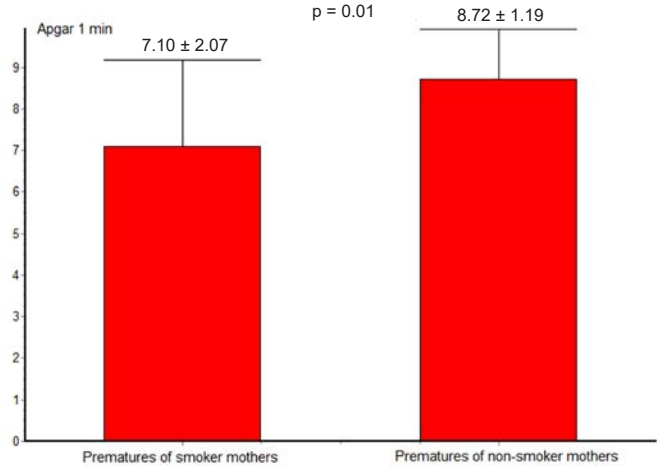

FIGURE 3. The Apgar score at 1 minute in the premature newborns of smoking vs. non-smoking mothers

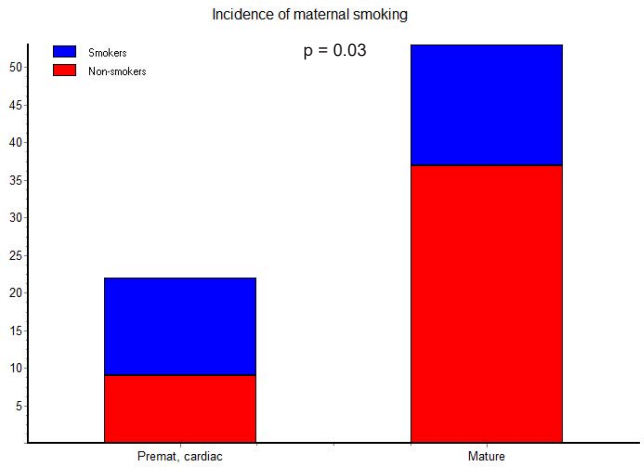

FIGURE 4. Incidence of maternal smoking in the control vs. pathology group (premature and cardiac)

DISCUSSIONS

Pregnancy is characterized by increased oxidative stress and lipid peroxidation compared with the non-pregnant state.[17] A diet rich in fruits, vegetables, and vitamins with antioxidant capacity can counteract the oxidative damage. In their study, Mathews *et al.* conclude that dietary antioxidant intake during pregnancy is inadequate.[18] Alberti-Fidanza *et al.* found that there is a transient imbalance between higher antioxidant requirements and intake during pregnancy. This is evolving gradually and progressively, regardless of changes in maternal diet.[19]

Preterm neonates have an immature antioxidant defense system, so we can assume that most of the complications are related to this immature antioxidant defense mechanism in association with an immature immune system and insufficient fetal maturity. It has been found that neonates exhibit higher oxidative stress than the mother herself during labor.[7]

According to a study by Arguelles *et al.*, newborns of smoking mothers had reduced antioxidant capacity and increased risk for lipid and protein peroxidation due to increased oxidative stress. The authors did not find statistically significant differences in the concentration of oxidative stress biomarkers during different birth types. They also concluded that even if the former smoker mother did not smoke during pregnancy, her oxidative stress state was increased, and there was a 14.3-fold higher possibility for lipid peroxidation. The mother's increased oxidative state produced by smoking showed a similar increase in the neonate's oxidative state. In accordance with other authors, the consequences of smoking impact fetal development, leading to intrauterine growth retardation.[4] Although our study did not have the power to demonstrate significant differences regarding weight at birth among different subgroups related to smoking status, it does not mean that smoking had no effect on fetal development. The exact assessment of the consequences of smoking on fetal development is to determine the parameters of oxidative stress and its effects on lipid peroxidation. However, our study showed that smoking had a negative effect on the Apgar score, which was lower in the subgroup of smoking mothers from the premature group. An association of the two risk factors (prematurity and smoking) may aggravate the postnatal outcomes of the newborn.

TABLE 3. Baseline characteristics of the study groups – maternal history

Characteristics	Control group (n = 60)	Premature group (n = 21)	Cardiac group (n = 8)
Maternal smoking*			
Yes	16 (26.66%)	9 (42.85%)	4 (50.00%)
No	37 (61.66%)	8 (38.09%)	4 (50.00%)
No response	7 (11.66%)	4 (19.04%)	0 (0.00%)
Dietary supplement*	51 (85%)	14 (66.67%)	3 (37.50%)
Yes	35 (58.33%)	10 (47.61%)	7 (87.50%)
No	16 (26.66%)	7 (33.33%)	1 (12.50%)
No response	9 (15.00%)	4 (19.04%)	0 (0.00%)
Stress*			
Yes (low/medium/high)	28/14/3 (75%)	11/4/0 (71.42%)	4/1/0 (62.50%)
No	7 (11.66%)	5 (23.80%)	2 (25.00)
No response	8 (13.33%)	1 (4.76%)	1 (12.50%)
Maternal pathology			
Yes	35 (58.33%)	18 (85.71%)	7 (87.5%)
No	25	2	1

* Exclusion criteria to be included to statistical evaluation: no response was given

According to Karacor *et al.*, oxidative stress markers were elevated in oxytocin-induced labor, but this had no effect on the Apgar score.[17] Our study also included several oxytocin-induced deliveries. According to Negi *et al.*, intrauterine growth retardation associated with oxidative stress has a negative effect on the development of fetal antioxidant defense mechanisms. They also showed that non-enzymatic antioxidant (e.g., vitamin A, E, C) levels in the cord blood of preterm low-birth-weight newborns were significantly lower compared with full-term newborns. According to their observation, these micronutrients can transform oxidative status and thus may extend the pregnancy to full term, or may prevent lipid, protein, and DNA damage.[20] We did not observe this protective effect of the antioxidant dietary supplements in our study group. The observation of Negi *et al.* was in accordance with the one made by Howlader *et al.*, who also concluded that there were increased levels of lipid peroxides and a decrease in the concentration of antioxidants such as vitamin C in case of preeclampsia.[21]

Knowing these facts, our exclusion criteria were based on excluding subjects from the control group with preexisting pathology that can enhance oxidative stress (hypertension, diabetes mellitus, hypothyroidism) in pregnancy, when oxidative stress is proportionally higher compared to non-pregnant status.

Study limitations

This study has the limitation of a small sample size (n = 21) in the premature group, and the association needs further investigation on a larger scale. Another limitation of the study is that data regarding smoking status was obtained by questionnaires filled in by the pregnant women, and there might be differences between the reported number of smoked cigarettes and their real smoking habits.

CONCLUSIONS

The Apgar score was lower in case of combined risk factors (smoking and poor antioxidant mechanisms). We also observed that smoking had a negative effect on the outcome of the newborn in case of the premature and cardiac groups. The prevention of smoking during pregnancy could be beneficial in reducing fetal exposure to increased oxidative stress.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Gitto E, Pellegrino S, D'Arrigo S, et al. Oxidative stress in resuscitation and in ventilation of newborns. *Eur Respir J*. 2009;34:1461-1469.
2. Haynes RL, Folkerth RD, Keefe RJ, et al. Nitrosative and oxidative injury to premyelinating oligodendrocytes in periventricular leukomalacia. *J Neuropathol Exp Neurol*. 2003;62:441-450.
3. Shobeiri F, Ranjbar A, Alizadeh FG, Nazari M. Salivary, plasma and cord blood oxidative stress biomarkers in mother and neonate: a combined analgesia concern. *Journal of Postgraduate Medical Institute (Peshawar - Pakistan)*. 2016;3118-24.
4. Arguelles S, Machado MJ, Ayala A, et al. Correlation between circulating biomarkers of oxidative stress of maternal and umbilical cord blood at birth. *Free Radical Research*. 2006;40:565-570.
5. Luo ZC, Fraser WD, Julien P, et al. Tracing the origins of "fetal origins" of adult diseases: programming by oxidative stress? *Med Hypotheses*. 2009;74:318-332.
6. Wilinska M, Borszewska-Lornacka MK, Niemiec T, et al. Oxidative stress and total antioxidant status in term newborns and their mothers. *Annals of Agricultural and Environmental Medicine*. 2015;22:736-740.
7. Chitra M, Mathangi DC, Johnson P. Oxidative stress during spontaneous vaginal delivery: comparison between maternal and neonatal oxidative status. *Indian Journal of Neonatal Medicine and Research*. 2017;5:PO16-PO21.
8. Turpeinen AM, Basu S, Mutanen M. A high linoleic acid diet increases oxidative stress in vivo and effects nitric oxide metabolism in humans. *Prostaglandines Leukot Essent Fatty Acids*. 1998;59:229-233
9. Maziere C, Dantin F, Conte MA, et al. Polyunsaturated fatty acid enrichment enhances endothelial cell-induced low density-lipoprotein peroxidation. *Biochem J*. 1998;336:57-62.
10. Burke BS. Diet and nutrition during pregnancy. *Am J Nutr*. 1952;11:1378-1380.
11. Clausen T, Slott M, Solvoll K, Drevon CA, Vollset SE, Henriksen T. High intake of energy, sucrose and polyunsaturated fatty acids is associated with increased risk of preeclampsia. *Am J Obstet Gynecol*. 2001;185:451-458.
12. Scholl OT, Leskiw M, Chen X, Sims M, Stein PT. Oxidative stress, diet, and the etiology of preeclampsia. *Am J Clin Nutr*. 2005;81:1390-1396.
13. Ricketts SA, Murray EK, Schwalberg R. Reducing low birth weight by resolving risks: results from Colorado's prenatal plus program. *Am J Public Health*. 2005;95:1952-1957.
14. Salihu HM, Sharma PP, Getahun D, et al. Prenatal tobacco use and risk of stillbirth: a case-control and bidirectional case-crossover study. *Nicotine Tob Res*. 2008;10:159-166.
15. Huang ZG, Griffioen KJ, Wang X, et al. Differential control of central cardiorespiratory interactions by hypercapnia and the effect of prenatal nicotine. *J Neurosci*. 2006;26:21-29.
16. Knopik VS. Maternal smoking during pregnancy and child outcomes: real or spurious effect? *Dev Neuropsychol*. 2009;34:1-36.
17. Karacor T, Sak S, Basaranoglu S, et al. Assessment of oxidative stress markers in cord blood of newborns to patients with oxytocin-induced labor. *J Obstet Gynaecol Res*. 2017;43:860-865.
18. Mathews F, Yudkin P, Smith RF, et al. Nutrient intakes during pregnancy: the influence of smoking status and age. *J Epidemiol Community Health*. 2000;54:2317-2318.
19. Alberti-Fidanza A, Di Renzo GC, Burini G, et al. Diet during pregnancy and total antioxidant capacity in maternal and umbilical cord blood. *J Matern Fetal Neonatal Med*. 2002;12:59-63.
20. Negi R, Pande D, Kumar A, et al. Evaluation of biomarkers of oxidative stress and antioxidant capacity in the cord blood of preterm low birth weight neonates. *J Matern Fetal Neonatal Med*. 2012,25:1338-1341.
21. Howlander ZH, Parveen S, Tamanna S, et al. Oxidative stress and antioxidant status in neonates born to pre-eclamptic mother. *J Trop Pediatr*. 2009;55:363-367.

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ORIGINAL RESEARCH

GENERAL SURGERY // HEALTH ECONOMICS

Primary Medical Effects and Economic Impact of Anastomotic Leakage in Patients with Colorectal Cancer. A Middle-Income Country Perspective

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ABSTRACT

Introduction: Anastomotic leakage is one of the most serious surgical complications that can increase the potential postoperative morbidity, mortality, and overall costs of patient care. Aim of study: To assess the economic burden of anastomotic leakage and to estimate its major clinical effects on patient evaluation. **Materials and methods:** We retrospectively reviewed single-surgeon data about patients who underwent surgical intervention for colorectal cancer at the 2nd Surgery Department of the Mureș County Emergency Clinical Hospital between January 2019 and July 2020. We assessed general characteristics, surgical data, postoperative information, oncologic results, and financial aspects for each patient. Depending on the presence of anastomotic leakage, patients were divided into two groups: a study group (SG) – patients with postoperative anastomotic failure, and a control Group (CG) – patients without postoperative anastomotic failure. **Results:** Patients with anastomotic leakage presented increased use of antibiotics, greater number of surgical reinterventions, longer period of intensive care treatment, prolonged hospitalization, increased overall costs, and significantly greater financial loss for the hospital. **Conclusion:** Anastomotic leakage leads to important negative effects, including longer hospitalization, prolonged intensive care unit stay, greater incidence of surgical reintervention, increased hospitalization costs, and significant financial loss.

Keywords: anastomotic leakage, economic burden, medical effects, hospitalization costs

INTRODUCTION

Anastomotic leakage is one of the most serious surgical complications that can occur in the postoperative period. Studies report rates from 1.5% to 16% for anastomotic leaks (ALs) following colorectal cancer surgery. These complications increase postoperative morbidity, mortality, and the overall costs of pa-

tient care. Clinical manifestations of ALs will often lead to hospital readmission, causing considerable additional medical and financial burden on both patients and healthcare providers. However, the impact of ALs on hospitalization costs varies across different economies, especially in low- and middle-income countries. Financial burden causes additional challenges due to the possibility of limited resources. Recently conducted studies have highlighted that ALs increase total hospitalization costs by 0.5–1.9 times. Therefore, a survey of their primary medical effects and financial consequences represents an important guide for health professionals.[1–5]

AIM OF STUDY

The primary objective of the study was to assess the economic burden of anastomotic leakage and to estimate its major medical effects throughout the patients' clinical evaluation.

MATERIALS AND METHODS

Study design

The study included 120 patients who underwent surgery for colorectal cancer at the 2nd Surgery Department of the Mureş County Emergency Clinical Hospital from Târgu Mureş between January 2019 and July 2020. In order to reduce the impact of various surgical habits or experience, only cases handled by the same surgical team were analyzed. An electronic database was created using the H3 Concept Healthcare Electronical System, including information about patient admission, diagnosis, laboratory and imaging investigations, surgical procedures, medication, materials used during hospital stay, and hospitalization costs. The system provides reliable information for several time periods: prior to admission, during admission, short-term follow-up, and readmissions. Exclusion criteria included age <18 years, surgery in emergency conditions, and all cases where anastomosis was not possible and stoma formation was required during the surgical intervention.

Variables and study groups

For each patient, multiple variables were evaluated:

- general characteristics: age, gender, tumor location, anemia at the time of admission;
- surgical assessment: main surgical procedure, protective stoma formation, anastomosis, execution of anastomosis, type of anastomosis, duration of surgery, mean intraoperative blood loss;
- postoperative data: anemia during follow-up, start of bowel motility, start of oral feeding, development of AL, onset of AL, debit of AL, surgical reintervention, intensive care unit (ICU) stay, length of hospital stay, 30-day readmission, length of secondary hospital stay, in-hospital mortality;
- oncologic outcome: local tumoral spread, distant metastasis, TNM staging;
- financial aspects: costs for hospital stay, laboratory tests, radiological investigations, surgical treatment, and medication; DRG index, hospital income, index hospitalization costs, hospital profit or loss.

Based on hemoglobin (Hb) levels, perioperative anemia was categorized into mild (Hb >11 g/dL), moderate (Hb 8–11 g/dL), and severe (Hb <8 g/dL). Return of bowel motility was categorized into average (1–4 days) and late return (>5 days). Oral feeding was categorized into early (on postoperative day 1–2) and late oral feeding (after the return of bowel motility). Based on the onset of AL, we distinguished early (1–4 days), moderate (5–10 days), and late (>30 days) occurrence of AL. For the classification of anastomotic failure, we used the grading system proposed by the International Study Group of Rectal Cancer: grade A – asymptomatic leakage; grade B – requires active intervention without relaparotomy; grade C – requires relaparotomy. Length of stay in the ICU was categorized as follows: without AL, short (1–2 days), and prolonged (>3 days). Hospitalization was categorized into primary or index hospitalization (during which the surgical intervention was performed in order to treat the colorectal cancer) and secondary hospitalization (following readmission for complications).

Depending on the presence of AL, patients were divided into two groups: a study group (SG) – patients with postoperative anastomotic failure; and a control group (CG) – patients who did not develop such a complication after surgical intervention.

Statistical analysis

Data were collected into an electronic database using Microsoft Excel. Statistical analysis was performed using GraphPad Instat software (GraphPad Software, Inc., San Diego, United States of America). Qualitative data were expressed as integer values and percentages, while quantitative results were expressed as mean and median, after normality testing was performed. The statistical difference

TABLE 1. Major medical effects of anastomotic leakage

	Patients with AL n = 12	Patients without AL n = 108	p value
Antibiotic use, n (%)			
Prophylactic	0 (0)	95 (87.96)	0.0001
Long-term treatment	12 (100)	13 (12.04)	0.0001
Necessity of relaparatomy, n (%)	9 (75)	7 (6.48)	0.0001
Stoma formation during reintervention, n (%)	9 (75)	0 (0)	–
Length of ICU stay			
No ICU stay	2 (16.67)	89 (82.41)	0.0001
1–2 days	6 (50)	13 (12.04)	0.0037
> 3 days	4 (33.33)	6 (5.56)	0.0090
Average length of index hospitalization, days	17.41	10.48	0.0001
In-hospital mortality, n (%)	3 (25)	4 (3.70)	0.0216
30-day readmission, n (%)	3 (25)	11 (10.18)	0.3914
Average length of second hospitalization, days	7.67	5.72	0.1001

AL – anastomotic leakage; ICU – intensive care unit; Index hospitalization – primary hospital stay prior to surgical intervention; Secondary hospitalization – hospital stay after readmission

between groups regarding quantitative data was calculated using Student's t test or Mann-Whitney test when appropriate. Categorical data was analyzed using Fisher's exact test. The level of statistical significance was set at a p value of 0.05, with a confidence interval of 95% for all calculated parameters.

RESULTS

A short summary of the major medical effects of anastomotic leakage is presented in Table 1.

Patients in the SG received prolonged antibiotic therapy during hospitalization, while patients in the CG received mostly prophylactic treatment (p = 0.0001). Surgical reintervention was also carried out in a higher proportion in patients from the SG (p = 0.0001), 75% of these patients requiring a second laparotomy in order to treat complications caused by the fistula. Most of these cases required anastomotic takedown and stoma formation. Regarding ICU stay, the majority of patients in the CG did not require intensive care treatment (p = 0.0001). On the other hand, patients who developed ALs spent longer periods in the

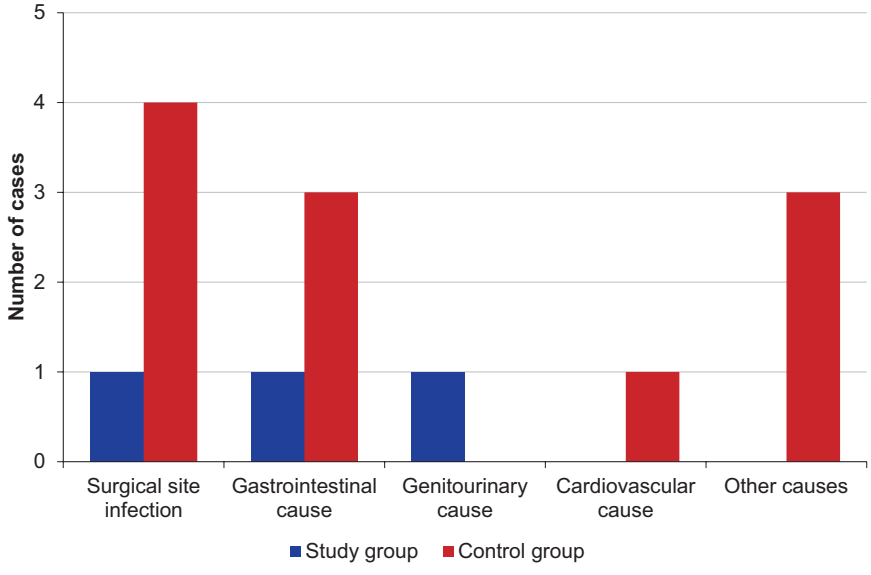

FIGURE 1. Primary reasons for 30-day readmission

TABLE 2. Financial aspects in patients with and without anastomotic leakage

	Patients with AL n = 12	Patients without AL n = 108	p value
Average costs for laboratory test	70.09	47.92	0.5260
Average costs for radiological invest.	5.94	4.06	0.0303
Average costs for surgical treatment	440.3	557.92	0.1400
Average costs for medication	308.49	208.82	0.0285
Average index hospitalization costs	1973.32	1181.97	0.0009
Average DRG of treated patients	3.69	3.31	0.3731
Average loss-profit/patient	–754.5	+45.6	0.0032

All values are calculated in EUR.

ICU (1–2 days p = 0.0037; >3 days p = 0.0090). Index hospitalization was also significantly longer (p = 0.0001) for patients from the SG, with an average of 17.41 days. There were no significant differences between the two groups regarding the length of secondary hospitalization. The primary cause for 30-day readmission varied in the two groups and included the following: surgical site infection (SG – 1, CG – 4), gastrointestinal cause (SG – 1, CG – 3), genitourinary cause (SG – 1, CG – 0), cardiovascular cause (SG – 0, CG – 1), and other cause (SG – 0, CG – 3) (Figure 1). In-hospital mortality was also significantly higher in patients with AL (p = 0.0216).

Results regarding the financial aspects are presented in Table 2.

While costs for laboratory tests and surgical treatment did not show important dissimilarities, costs for radiological examinations (p = 0.0303) and medication (p = 0.0285) were significantly higher in case of patients with ALs. The DRG-based case coefficient was nearly similar, without statistically important differences, while the index hospitalization costs were significantly higher for patients with anastomotic leakage (p = 0.0009). Furthermore, the presence of AL determined significant financial loss for the hospital budget (p = 0.0032). When analyzing each factor individually (Figure 2), we observed that prolonged ICU stay (p = 0.0458, OR = 4.98, RR = 1.8), surgical reintervention (p = 0.0111, OR = 5.333, RR = 1.9), anastomotic leakage (p = 0.0001, OR = 34.89, RR = 2.4), advanced stages of cancer (p = 0.033, OR = 2.65, RR = 1.6), perioperative anemia (p = 0.0522, OR = 7.294, RR = 1.9), tumors with distal localization (p = 0.0215, OR = 3.122, RR = 1.6), and advanced age (p = 0.0046, OR = 3.438, RR = 1.8) were independent risk factors contributing to the increase of hospitalization costs.

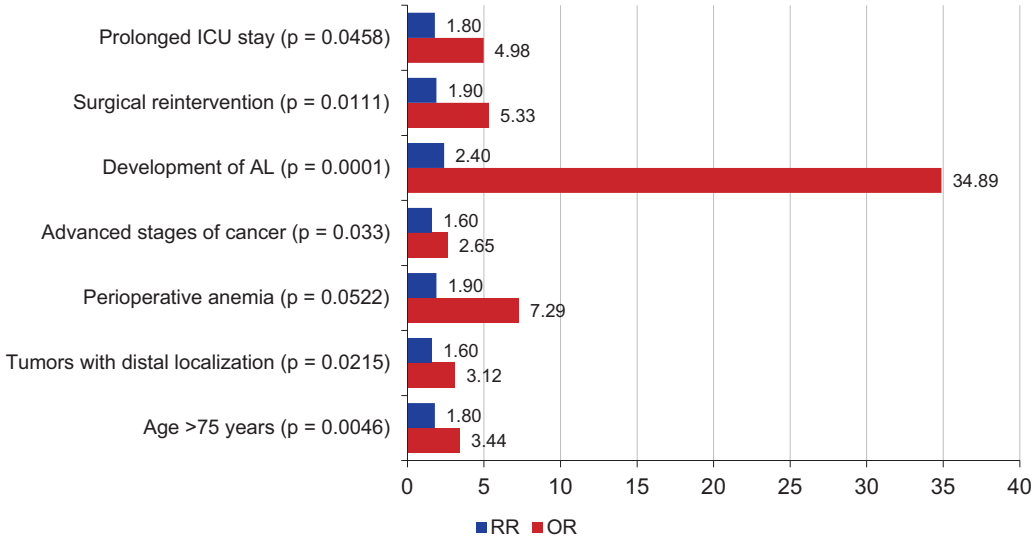

FIGURE 2. Factors independently affecting increase of hospitalization costs

DISCUSSIONS

Antibiotic usage

The present study found that in case of anastomotic leakage, the use of antibiotics increased significantly. Only 12.03 % of patients in the CG received sustained antibiotic treatment; the rest presented favorable evolution with prophylactic antibiotic therapy. All patients with anastomotic leakage required prolonged medication in order to treat the septic complications of AL. Ribeiro Jr *et al.* reported similar results, highlighting that ALs increased antibiotic use by nearly 70%.[6] Similar results were found in other studies as well.[7]

Surgical reintervention and quality of life

In the postoperative period, a second laparotomy was necessary in nine patients (75%) in the SG and seven patients (6.48%) in the CG. It can be stated that ALs had a strong influence on the surgical reintervention rate, causing additional stress in the healing process of patients. All C-grade ALs were operated, anastomotic takedown and stoma formation being applied in the majority of cases. Stoma formation has seriously affected the patients' quality of life, as confirmed by other, similar studies.[8,9]

Intensive care unit stay

In the present study, 83.33% of patients in the SG required ICU admission and treatment, compared to only 17.59% of patients from the CG. In a study based on 1,684 intestinal resections, Byrn *et al.* observed that the presence of ALs had a strong influence on the length of stay in the ICU.[10] Dale *et al.* also highlighted prolonged ICU stays in case of patients with anastomotic leakage.[11]

Hospitalization period and readmissions

Regarding the length of hospitalization, anastomotic leakage seemed to influence the index hospitalization in a significant manner. The hospitalization of patients with AL was one week longer on average compared to patients with anastomotic integrity. Hammond *et al.* also found a significantly longer hospitalization period.[12] The secondary hospitalization was similar among patients with and without AL. In contradiction with our results, several studies found that the secondary hospitalization was also significantly prolonged due to the presence of anastomotic leakage.[13]

We observed different reasons for hospital readmission in the two studied groups. The main reasons for hospital readmission for patients with anastomotic leakage were surgical site infection, urinary infection, and stenosis of the terminal colostomy. Meanwhile, in case of patients without AL in the postoperative period, surgical complications developed in only a few cases (bowel obstruction, surgical site infection). Other reasons for rehospitalization included medical conditions such as pneumonia, acute myocardial infarction, and abdominal pain (without surgical cause). Although twice as many patients with anastomotic leakage were forced to attend a second hospital admission (25%), the statistical analysis did not show significant differences between the two groups, probably due to the smaller sample size. Krell *et al.* found that hospital readmissions were more frequently caused by postoperative complications.[14] It is well known that the development of anastomotic leakage increases morbidity and mortality in a significantly manner. Many studies found that anastomotic leakage has a significant negative impact on the postoperative evolution of patients.[15,16]

Financial considerations

In terms of economic impact, total costs were considerably greater for patients with ALs compared to patients without this complication. The DRG-based case index did not differ notably; as a result, hospital income after a resolved case was almost identical in the two groups. Therefore, patients with anastomotic leakage produced a major loss for the hospital, with an average of €750 per patient. Meantime, hospital profit after a patient without complications was only €45 on average. Consequently, it is easy to understand that ALs have devastating economic consequences. Other studies presented similar results.[17,18] Multivariate analysis identified multiple factors independently affecting the elevation of hospitalization costs. Springer *et al.* found that ALs and the necessity of surgical reintervention significantly increased overall costs.[19] Furthermore, Macafee *et al.* identified advanced stages of cancer and distal tumor localization as potential factors contributing to excessive hospitalization costs,[20] while Feng *et al.* observed that perioperative anemia has significant effects on the financial balance.[21]

CONCLUSION

In conclusion, anastomotic leakage leads to important medical effects including longer hospitalization, prolonged intensive care unit stay, and greater incidence of surgical

reintervention. An important economic burden can also be noticed, increasing hospitalization costs by 1.66 times and resulting in significant financial loss for the hospital.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. Thomas MS, Margolin DA. Management of colorectal anastomotic leak. *Clin Colon Rectal Surg*. 2016;29:138-144.
2. La Regina D, Di Giuseppe M, Lucchelli M, et al. Financial impact of anastomotic leakage in colorectal surgery. *J Gastrointest Surg*. 2019;23:580-586.
3. Fouda E, El Nakeeb A, Magdy A, Hammad EA, Othman G, Farid M. Early detection of anastomotic leakage after elective low anterior resection. *J Gastrointest Surg*. 2011;15:137-144.
4. Ha GW, Kim JH, Lee MR. Oncologic impact of anastomotic leakage following colorectal cancer surgery: a systematic review and metanalysis. *Ann Surg Oncol*. 2017;24:3289-3299.
5. Wan Y, Lim S, Riebman J, Jamous N, Gao X. Clinical and economic burden associated with anastomotic leak after colorectal surgeries in the United Kingdom. *Gut*. 2014;63:A132.
6. Ribeiro U Jr, Tayar DO, Ribeiro RA, Andrade P, Junqueira SM Jr. The clinical and economic burden of colorectal anastomotic leaks: middle-income country perspective. *Gastroenterology Research and Practice*. 2019;2879049.
7. Kobayashi M, Mohri Y, Ohi M, et al. Risk factors for anastomotic leakage and favorable antimicrobial treatment as empirical therapy for intra-abdominal infection in patients undergoing colorectal surgery. *Surg Today*. 2014;44:487-493.
8. Fraccalvieri D, Biondo S, Saez J, et al. Management of colorectal anastomotic leakage: differences between salvage and anastomotic takedown. *Am J Surg*. 2012;204:671-676.
9. Anaraki F, Vafaie M, Behboo R, Maghsoodi N, Esmaeilpour S, Safaee A. Quality of life outcomes in patients living with stoma. *Indian J Palliat Care*. 2012;18:176-180.
10. Byrn JC, Schlager A, Divino CA, Weber KJ, Baril DT, Aufses AH Jr. The management of 38 anastomotic leaks after 1.684 intestinal resections. *Dis Colon Rectum*. 2006;49:1346-1353.
11. Dale CD, Mcloone P, Sloan B, et al. Critical care provision after colorectal cancer surgery. *BMC Anesthesiol*. 2016;16:94.
12. Hammond J, Lim S, Wan Y, Gao X, Patkar A. The burden of gastrointestinal anastomotic leaks: an evaluation of clinical and economic outcomes. *J Gastrointest Surg*. 2014;18:1176-1185.
13. Nikolian VC, Kamdar NS, Regenbogen SE, et al. Anastomotic leak after colorectal resection: A population-based study of risk factors and hospital variation. *Surgery*. 2017;161:1619-1627.
14. Krell RW, Girotti ME, Fritze D, Campbell DA, Hendren S. Hospital readmission after colectomy: a population based study. *J Am Coll Surg*. 2013;217:1070-1079.
15. Boström P, Haapamäki MM, Rutegård J, Matthiessen P, Rutegård M. Population-based cohort study of the impact on postoperative mortality of anastomotic leakage after anterior resection for rectal cancer. *BJS Open*. 2018;3:106-111.
16. Choudhuri AH, Uppal R. Predictors of septic shock following anastomotic leak after major gastrointestinal surgery: An audit from a tertiary care institute. *Indian J Crit Care Med*. 2013;17:298-303.
17. Lee SW, Gregory D, Cool CL. Clinical and economic burden of colorectal and bariatric anastomotic leaks. *Surg Endosc*. 2020;34:4374-4381.
18. Ashraf SQ, Burns EM, Jani A, et al. The economic impact of anastomotic leakage after anterior resections in English NHS hospitals: are we adequately remunerating them? *Colorectal Dis*. 2013;15:e190-198.
19. Springer JE, Doumouras AG, Saleh F, et al. Drivers of Inpatient Costs After Colorectal Surgery Within a Publicly Funded Healthcare System. *Dis Colon Rectum*. 2019;62:747-754.
20. Macafee DA, West J, Scholefield JH, Whynes DK. Hospital costs of colorectal cancer care. *Clin Med Oncol*. 2009;3:27-37.
21. Feng S, Greenberg J, Moloo H, Thavorn K, Mclsaac DI. Hospital cost associated with anemia in elective colorectal surgery: a historical cohort study. *Can J Anesth*. 2019;66:877-885.

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CLINICAL UPDATE

ENDOCRINOLOGY // DERMATOLOGY

Clinical Profiles of Thyroid Dermopathy: A Dermato-Endocrinological Perspective

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ABSTRACT

Thyroid disorders sometimes have extra-thyroidal manifestations. Hyperthyroidism is a clinical syndrome resulting from excessive secretion of thyroid hormones. The most common cause is Graves' disease. About 0.5–4.3% of patients with Graves' disease have an infiltrative dermopathy called thyroid dermopathy, which is due to excessive deposition of glycosaminoglycans from activated fibroblasts. Skin fibroblasts are activated by thyroid stimulating hormone receptor antibodies the whole process being initiated by T lymphocytes. Rarely, thyroid dermopathy is also found in other thyroid disorders such as Hashimoto thyroiditis. The diffuse non-pitting edema variant is the most common clinical presentation. Other variants include the nodular, plaque, mixed, and elephantiasis types. Usually, the main concerns of the patients are cosmetic, discomfort, and difficulty in wearing shoes. Thyroid dermopathy usually presents after the diagnosis of Graves' disease, but it may also present together or sometime after this condition. Rarely, thyroid dermopathy presents before the diagnosis of Graves' disease is made. Apart from the shin and feet, other sites that can be affected include the arms, forearms, back, thighs, pinna, and nose. The management is multidisciplinary, involving dermatologists and endocrinologists. Usually, controlling the thyroid dysfunction does not translate into regression of the skin lesions. However, many patients have their thyroid dermopathy regress spontaneously, while others usually require local therapy. Other therapeutic options include systemic therapy such as pentoxifylline, compressive physiotherapy, and surgery.

Keywords: thyroid dermopathy, clinical profile, dermato-endocrinological perspective

INTRODUCTION

The thyroid gland is a butterfly-shaped endocrine organ located in the neck. It produces thyroid hormones, which regulate metabolic activities in the body. Hyperthyroidism is a clinical syndrome caused by excessive production and secretion of thyroid hormones. The commonly reported clinical features are heat intolerance, anxiety, excessive sweating, palpitation, fatigue, hyperdefecation, and menstrual disturbance.[1] Graves' disease, an autoimmune disorder, is the most common cause of hyperthyroidism.[2] Occasionally, it affects other organs such as the eyes and the skin.

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Thyroid dermopathy, sometimes called pretibial myxedema, is found in about 0.5–4.3% of patients with Graves' disease.[3] It is an infiltrative dermopathy diagnosed in the presence of typical symptoms and signs, biochemical evidence of thyroid dysfunction or evidence of the characteristic autoimmune markers, as well as pathological findings in the skin.[3] It manifests in various ways, affecting the skin of different parts of the body.

PATHOGENESIS

In genetically predisposed individuals, thyroid dermopathy results from an immunological cross-reaction occurring in the skin, where thyroid stimulating hormone (TSH) receptor antibodies stimulate the fibroblasts in the connective tissue.[4] In vitro studies have demonstrated that fibroblasts in the skin and orbit express TSH receptors on their cell surface.[5]

Activation of the fibroblasts make them overproduce glycosaminoglycans, leading to fluid retention in the connective tissue of the skin. The antigen-antibody response is initiated by the activation of T lymphocytes. Other factors, such as localized trauma and venous stasis, have also been suggested to contribute to the development of thyroid dermopathy.

Histopathologically, reduced collagen fibers, extensive mucin deposition, reduced elastic tissue, and edema are the characteristic findings.[3] Other rarely documented pathological features include hyperkeratosis, acanthosis, and papillomatosis.[3] The pathogenesis of thyroid dermopathy is summarized in Figure 1.

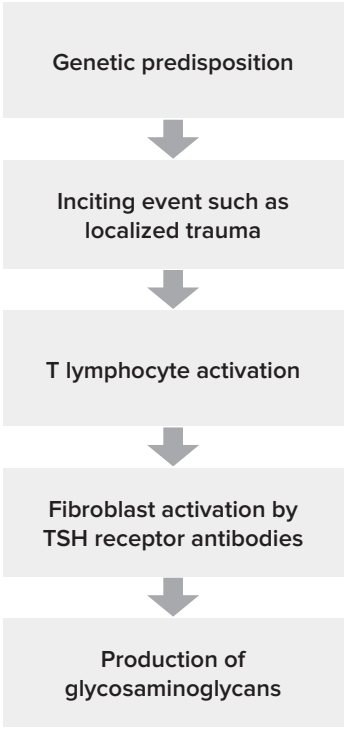

FIGURE 1. The pathogenesis of thyroid dermopathy

RISK FACTORS

Risk factors for the development of thyroid dermopathy are not known. However, some researchers have suggested that previous radioiodine therapy, smoking, thyroid hormonal imbalance, as well as the presence of Graves' orbitopathy could predispose an individual to developing thyroid dermopathy.[7]

SITES OF THYROID DERMOPATHY

The term 'pretibial myxoedema' is less favored to thyroid dermopathy because the skin lesions are found in many other areas apart from the pretibial area. The most common sites documented in the literature and their frequency are illustrated in Table 1.[3] The reasons for lower limb predilection are not known. Some hypotheses include gravitational forces and a higher concentration of fibroblasts.[3]

CLINICAL PRESENTATION OF THYROID DERMOPATHY

Thyroid dermopathy is found mostly in Graves' disease but it has also been documented in patients with Hashimoto thyroiditis, atrophic thyroiditis, and in euthyroid individuals.[6] It is also more frequently seen in females compared to males. This may be due to the fact that autoimmune thyroid disorders are generally more common in females.[3] The main reasons for presentation include cosmetic complaints, discomfort, and difficulty in wearing shoes.

TABLE 1. Sites of thyroid dermopathy and their frequencies

Site	Frequency
Pretibial only	94%
Pretibial + feet	4%
Pretibial + upper extremities	<1%
Arms	<1%
Preradial forearms	<1%
Upper back	<1%
Shoulder	<1%
Pinnae	<0.5%
Nose	<0.01%
Thigh	<0.01%

The temporal profile of thyroid dermopathy in relation with Graves' disease is variable. Usually, it occurs after the diagnosis of Graves' disease but it may also predate it, or they may present concurrently.[3] Often, it occurs after the onset of Graves' orbitopathy, another manifestation of Graves' disease with similar pathophysiology.

Thyroid dermopathy needs to be differentiated from lichen planus, stasis dermatitis, lichen simplex chronicus, and necrobiosis lipoidica. Thus, a review by a dermatologist is crucial in the management of thyroid dermopathy.

TYPES OF THYROID DERMOPATHY

Thyroid dermopathy presents in various forms. The various clinical variants are discussed briefly below. Figure 2 illustrates the clinical variants of thyroid dermopathy and their frequencies, based on the findings of a retrospective study conducted by Sabanova *et al.*[8]

The diffuse thyroid dermopathy variant usually presents as non-pitting edema. It is the most common variant and is characterized by induration of the skin giving the classical 'peau d' orange' sign.[3] Some patients, in addition to the peau d'orange sign, also have diffuse hyperpigmented papules. Other variants are nodular and diffuse plaque types. Rarely, patients present with mixed nodular and plaque type. The elephantiasis variant, which presents like the late stage of lymphatic filariasis, has also been documented.[8] This is often accompanied by significant functional disability. The complications of thyroid dermopathy include psychological distress, superimposed bacterial infection, recurrence, and entrapment neuropathy causing foot drop.[3]

TREATMENT OF THYROID DERMOPATHY

The treatment of thyroid dermopathy requires a collaborative effort from the endocrinologist and the dermatologist. The treatment is often challenging; in many patients, the duration of treatment requires months before regression begins, but they mostly regress eventually.[4] Studies have shown that control of the thyroid dysfunction may not necessarily lead to the regression of thyroid dermopathy.[2] Topical steroids, and in some instances intralesional steroid, with or without occlusion, have been used with some moderate response. In some severe variants, compressive physiotherapy as well as surgery have been adopted as therapeutic options. Newer therapies include the use of pentoxifylline and somatostatin analogues to reduce the production of glycosaminoglycans. However, there is a paucity of data on the outcomes of these treatment modalities. In resistant cases, intravenous globulins or plasmapheresis have been attempted.[3]

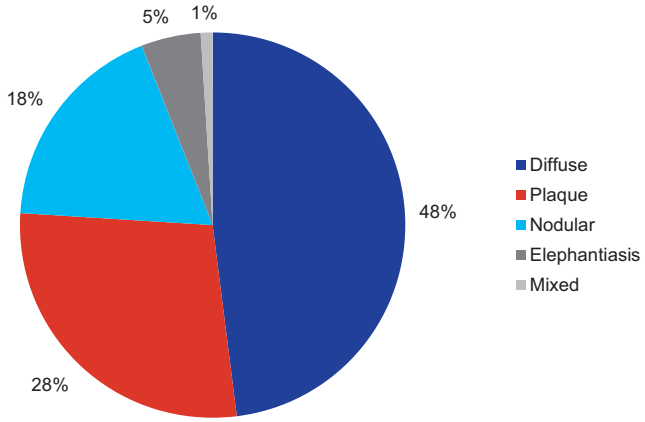

FIGURE 2. Thyroid dermopathy variants and their frequencies[8]

PROGNOSIS

Largely, the prognosis of thyroid dermopathy is good. A study done by Schwartz *et al.*, assessing the long-term outcome of thyroid dermopathy, reported that close to half of the patients in the series regressed spontaneously, without requiring any intervention.[4] The majority of patients requiring therapy had only topical steroids or intralesional steroids, and most of them had a significant response to therapy in form of partial or complete regression.

CONCLUSIONS

Thyroid dermopathy is an infiltrative dermopathy caused by the accumulation of glycosaminoglycans deposited by skin fibroblasts activated by TSH receptor-stimulating antibodies. They are found in less than 5% of Graves' disease patients. The most frequent presentation is diffuse non-pitting edema. Other variants include nodular, plaque, elephantiasis, and mixed types. The most common sites involved are the pretibial area and feet, while other sites, such as the upper limbs, back, and thighs, are rarely involved. Thyroid dermopathy resolves spontaneously in many patients. Local therapy is the most commonly employed treatment modality, and management requires inputs from the dermatologist and the endocrinologist.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Adeleye JO, Emuze ME, Azeez TA, Esan A, Akande TO, Balogun WO. Clinical profiles of males with Graves' disease: a two year review in a tertiary hospital in Nigeria. *J Clin Biomed Res*. 2020;2:1-2.
2. Samuels MH. Most patients with Graves' disease treated with additional anti-thyroid drugs eventually require additional therapies. *Clin Thyroidol*. 2020;32:9-11.
3. Dhali TK, Chahar M. Thyroid dermopathy – a diagnostic clue of hidden hyperthyroidism. *Dermatoendocrinol*. 2014;6:e981078.
4. Schwartz KM, Fatourechi V, Ahmed DD, Pond GR. Dermopathy of Graves' disease (pretibial myxedema): long-term outcome. *J Clin Endocrinol Metab*. 2002;87:438-446.
5. Davies T, Marians R, Latif R. The TSH receptor reveals itself. *J Clin Invest*. 2002;110:161-164.
6. Nair PA, Mishra A, Chaudhary A. A pretibial myxedema associated with euthyroid Hashimoto thyroiditis: a case report. *J Clin Diagn Res*. 2014;8:1-2.
7. Peacey SR, Flemming L, Messenger A, Weetman AP. Is Graves' dermopathy a generalized disorder? *Thyroid*. 1996;6:41-45.
8. Sabanova E, Fadeyev V, Lvov A. Thyroid dermopathy: clinical features in Graves' disease. *Endocrine Abstracts*. 2019;63:1217.

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CLINICAL UPDATE

CARDIOLOGY // INFECTIOUS DISEASES

Cessation of Renin-Angiotensin System Antagonists During the SARS-CoV-2 Pandemic – Do We Have the Evidence?

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ABSTRACT

The aim of this review is to provide a short update on whether treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has beneficial or harmful effects in patients infected with SARS-CoV-2. Epidemiological studies have shown that SARS-CoV-2 infects all age groups, presenting a higher incidence in elderly patients with various comorbidities such as hypertension, diabetes mellitus, and cardiovascular diseases. A large proportion of these patients are treated with ACEIs and ARBs. Since it has been demonstrated that SARS-CoV-2 uses angiotensin converting enzyme type 2 (ACE2) as an entry point into host cells, it is important to know whether ACEIs and ARBs could modify the expression of this enzyme, and thus promote the viral infection. Animal studies and a few studies in humans have shown that renin angiotensin system (RAS) inhibitors increase tissue expression of ACE2, but with potentially beneficial effects. In this context, it is imperative to provide appropriate guidance for clinicians and patients. The major cardiology associations across the world have released statements in which they recommend healthcare providers and patients to continue their treatments for hypertension and heart failure as prescribed.

Keywords: COVID-19, ACE2, angiotensin-1-7, RAS inhibitors

INTRODUCTION

In December 2019, a number of cases of atypical pneumonia with an unknown pathogen were reported in Wuhan City, Hubei Province, China. The pathogen was later identified as a member of the Coronaviridae family and was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), while the disease caused is called coronavirus disease 2019 (COVID-19). The severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome-related coronavirus (MERS-CoV) are also part of this family. As a side note, this is the third consecutive decade in which a coronavirus crosses species to infect humans (SARS-CoV has infected more than 8,000 people in

2002–2003, and MERS-CoV has infected more than 2,500 people since 2012).[1,2] On January 13, the first case of COVID-19 infection was reported outside of China, while in Europe, the first case was reported on January 24. Due to the high rate of contagion and the aggressiveness of the disease, but also due to the lack of reactivity from the authorities, on March 11, the World Health Organization declared it a pandemic. Until the middle of June 2020, there were 7,670,880 confirmed cases and 427,097 deaths, across 311 countries worldwide.[3] Unfortunately, in the absence of an effective treatment or medical intervention, attempts to control the spread of the infection have relied on non-pharmaceutical intervention. This includes promotion of personal hygiene, social distancing, closing of schools and other public places, identification of infected cases and their contacts, and also preparation of health systems for a wave of severely ill patients who require intensive care and isolation.[4]

From the beginning of the pandemic it was shown that positive patients were more likely to have hypertension, diabetes mellitus, and other cardiovascular diseases, and had a clear indication for treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). This had given rise to several concerns because SARS-CoV-2 uses angiotensin-converting enzyme type 2 (ACE2) to enter the host cells. Also, renin angiotensin system (RAS) inhibitors increase the expression of ACE2, presumably resulting in higher infectivity of SARS-CoV-2, with development of a more severe form of the disease.[5,6] Because of these hypotheses, the rapidly evolving nature of the infection, and also panic spread via news and social media, official statements based on medical evidence were necessary for both clinicians and patients.

The aim of this paper is to offer a brief look at the current evidence regarding the continuation or interruption of treatment with ACEIs and ARBs in the context of the COVID-19 pandemic.

CLINICAL PROFILE OF PATIENTS THAT ARE VULNERABLE TO COVID-19 INFECTION AND COMPLICATIONS

Initial epidemiological studies have shown that SARS-CoV-2 infects all age groups, but elderly male patients with comorbidities, especially cardiovascular diseases, hypertension, or diabetes have a higher risk of developing a more severe form, requiring admission to the intensive care unit and mechanical ventilation.[7,8] An observational study on 8,910 patients with COVID-19 found that old age, coronary heart disease, heart failure, a history of cardiac arrhythmias, chronic obstructive pulmonary disease, and smoking were associated with a higher risk of in-hospital death.[9] In this context, many clinicians and patients had become aware of the possible interrelation between SARS-CoV-2 and the RAS. Due to the high global prevalence of hypertension, estimated at 1.13 billion in 2015, a high number of patients are likely be treated with RAS antagonists (ACEIs or ARBs).[10] The majority of studies regarding COVID-19 patients did not take into account the treatment for various comorbidities, and therefore the number of patients taking ACEIs or ARBs is unclear. However, two studies have shown that 15–20% of hospitalized patients were on treatment with ACEIs or ARBs, and about 50% of them discontinued treatment during hospitalization.[9,11]

WHAT IS THE LINK BETWEEN THE RAS AND SARS-CoV-2?

The RAS plays a central role in blood pressure regulation. Renin is an enzyme that is synthesized and released by the juxtaglomerular cells in response to decreased blood pressure and low sodium levels, or due to an increased activation of the sympathetic nervous system. Renin converts the enzymatically inactive angiotensinogen to angiotensin I, which is transformed into angiotensin II by the angiotensin-converting enzyme (ACE), present in the endothelium of lung vessels. Angiotensin II is a strong vasoconstrictor, particularly at the level of arterioles, acting on both the short- and long-term regulation of blood pressure and increasing peripheral vascular resistance. Angiotensin II also reduces sodium excretion by stimulating the release of aldosterone. Besides hemodynamic effects, angiotensin II stimulates the inflammatory response and promotes the generation of reactive oxygen species.[12] Angiotensin II is then converted to angiotensin-1-7 (Ang-1-7) by the membrane-bound ACE 2. Ang-1-7 causes vasodilation and presents anti-inflammatory and antifibrotic effects. Thus, ACE2 has two effects: reducing plasma concentrations of angiotensin II (decreasing vasoconstriction) and production of Ang-1-7 (increasing vasodilation).[13] Despite its beneficial effects, ACE2 has a dark side: SARS-CoV-2 uses this enzyme for gaining access into host cells. Binding and entry of SARS-CoV-2 is facilitated by attachment between the S (spike) protein located on the viral envelope and the enzymatic domain of ACE2.[14] However, a cofactor represented by the serine protease TMPRSS2 is needed for priming the S protein and activating the entry process.[15,16] Expression of both ACE2 and TMPRSS2 has been found in human nasal and respiratory tissues, bronchial epithelium, and type II alveolar cells.[17]

Thus, ACE2 may be considered the link between the RAS and SARS-CoV-2. However, the question still remains whether ACEIs and ARBs can influence the concentration of ACE2 and modify the course of SARS-CoV2 infection. ACEIs and ARBs are first-choice medication used for the treatment of hypertension and heart failure. In the past few months, the usefulness of RAS inhibitors has become an issue due to lack of proper clinical data on their effects in the setting of COVID-19. The main concern is that ACEIs or ARBs could increase the level of ACE2, leading to a higher number of viral entry points and increasing the susceptibility to infection or severity of the disease. The dilemma arose from the fact that increased levels of ACE2 reduce inflammation and can lead to a milder form of lung injury. Currently, there are two hypotheses regarding this mechanism. One states that RAS inhibition may have a harmful effect by increasing ACE2 levels and thereby promoting viral entry. The second hypothesis claims that RAS inhibition decreases angiotensin II synthesis and using ARB prevents angiotensin II from binding to angiotensin II type I receptor (AT1R) and also stabilizes the AT1R-ACE2 complex. This is subsequently preventing ACE2 internalization and degradation, with a weaker inflammatory response and attenuated lung injury.[18] These classes of medications do not interact directly with ACE2 because they do not bind and inhibit the active site of the enzyme, but there has been significant evidence in animal studies that showed increased expression of ACE2 after treatment with ARBs and ACEIs.[19,20] Angiotensin II treatment promoted ACE2 internalization, leading to a significant reduction in

TABLE 1. Outcomes of the main studies investigating the relationship between Sars-CoV-2 infection and the use of ACE inhibitors or angiotensin receptor blockers

Study	Population	Aim	Finding	Commentary
Mehra *et al*.[9]	8,910 patients who were discharged alive or died	Relationship of cardiovascular disease and drug therapy with in-hospital death among hospitalized patients with COVID-19	No increased risk of in-hospital death was found to be associated with the use of ACEIs or ARBs	Factors associated with increased risk of in-hospital death: >65 years, coronary artery disease, heart failure, cardiac arrhythmia, chronic obstructive pulmonary disease, current smoking
Meng *et al*.[32]	51 positive patients with hypertension	Ability of RAS inhibitors to protect against COVID-19 in patients with hypertension	Therapy with ACEIs or ARBs was associated with decreased viral load	
Mancia *et al*.[33]	6,272 positive patients 30,759 controls	Association between the use of RAS inhibitors and susceptibility to COVID-19	ACEIs and ARBs were not associated with the risk for COVID-19 infection	Use of ACEIs or ARBs did not show any association with mortality in positive patients
Reynolds *et al*.[34]	12,594 patients tested for COVID-19 and taking antihypertensive drugs	Relation between five classes of antihypertensive drugs (ACEI, ARB, BB, CCB, thiazide diuretics) and likelihood of a positive test	No class of antihypertension drugs was associated with an increase in the risk for testing positive	
Mehta *et al*.[35]	18,472 tested for COVID-19	Association between use of ACEIs or ARBs with testing positive for COVID-19	No association between ACEI or ARB use and COVID-19 test positivity	
de Abajo *et al*.[36]	1,139 positive patients11,390 controls	Use of RAS inhibitors and risk for admission to hospital in COVID-19 patients	RAS inhibitors did not increase risk of COVID-19 requiring admission	Patients with diabetes mellitus and treatment with RAS inhibitors had a lower risk for hospital admission
Khera *et al*.[37]	a) 853 positive outpatients receiving ACEIs or ARBs vs. 853 positive outpatients receiving other antihypertensive drugs	Use of ACEIs or ARBs and risk for hospitalization	Patients receiving ACEIs were less frequently hospitalized than those receiving other antihypertensive drugs. There was no significant association between ARB therapy and hospitalization.	
	b) 1,731 COVID-19 patients taking ACEIs and 1,580 COVID-19 patients taking ARBs matched to COVID-19 patients taking other antihypertensive drugs	Mortality in inpatient cohort receiving ACEIs or ARBs vs. inpatient cohort taking other antihypertensive drugs	Mortality did not differ between inpatient groups	

its enzymatic activity on the cell membrane. Losartan not only prevented internalization and degradation of ACE2, but also increased its expression 3-fold.[21] In two lung injury animal models, the activation of angiotensin type 1 receptors had led to increased intensity of tissue injury, while a marked signaling of the ACE2 system has reduced the harmful effects.[19,22] Another study showed that in mice, gene expression of ACE2 was increased 5-fold and 3-fold after treatment with lisinopril and losartan, respectively.[13] Of note, in mice, the loss of ACE is associated with resistance to SARS-CoV-2 infection, but also with increased vascular permeability, edema, leucocyte infiltration, and lung injury.[19,20] Conversely, overexpression of the ACE2 gene favored a better outcome after myocardial infarction in remodeling and improving ejection fraction.[23,24]

In humans, the effects of RAS inhibitors on the activity of ACE2 and Ang-1-7 are scarce. The blockade of AT1R, achieved by the administration of losartan or olmesartan, was accompanied by significant upregulation of ACE2 expression and increased levels of Ang-1-7.[25] Similarly, in another study, Ang-1-7 levels were not modified after initial treatment with captopril in patients with hypertension, but after exposure to captopril for 6 months, the level of ANG-1-7 increased.[26] The majority of data regarding the effect of RAS inhibitors on ACE2 expression was acquired from preclinical models and may not always translate to human physiology. Although ACE2 is insensitive to ACEIs, studies have shown that ACEI treatment in patients with viral pneumonia was associated with improved outcomes.[27–30] Furthermore, treatment with RAS inhibitors was associated with a reduction in viral load. This was probably an indirect effect of these drugs, resulting from the regulation of the immune response and inhibition of the inflammatory pathways rather than due to a direct blockage of virus replication.[31,32]

In several studies, treatment with ACEIs or ARBs was not associated either with a higher incidence of COVID-19 infection, or with more severe forms of infection or worse outcomes. One study even showed that the group of patients taking ACEIs/ARBs had a lower risk of mortality compared to controls, who have been prescribed a different anti-hypertensive regimen.[9,32–37]

Table 1 shows the main results of the studies investigating the link between ACE inhibition and SARS-CoV-2 infection.

The effects of treatment with ACEIs/ARBs in patients infected with SARS-CoV-2 are not fully understood. However, the cessation of RAS inhibitors, in the absence of a clear evidence or established reason, may have deleterious effects on the underlying cardiovascular disease.[38,39] Although these drugs produce an increase in ACE2 expression, thus promoting viral entry in host cells, it seems that patients on this medication have a lower risk for developing a more severe illness or worse outcomes. The Council of Hypertension of the ESC released a statement that strongly advises physicians and patients to continue treatment with their prescribed anti-hypertensive medication; there is no scientific evidence to demonstrate that treatment with ACEIs and ARBs should be discontinued in the presence of SARS-CoV-2 infection.[40] Also the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology are advocating that patients should continue treatment with RAS inhibitors prescribed for hypertension, ischemic heart disease, and heart failure. Changes in medications should be made only after careful assessment and based on the latest scientific evidence.[41]

CONCLUSIONS

Even though the major cardiology associations have released statements regarding the safety of continuing treatment with ACEIs and ARBs, the role of these drugs in SARS-CoV-2 infection is still under debate. There is a lack of solid scientific evidence regarding the discontinuation of treatments with RAS inhibitors in patients with COVID-19 and cardiovascular diseases. Although additional data may further shed light on the benefits and disadvantages of treatment with ACEIs and ARBs, physicians need to consider the undesirable results of discontinuing proven therapies in response to concerns that currently are not based on solid data.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. SARS (Severe Acute Respiratory Syndrome). Available at: https://www.who.int/ith/diseases/sars/en/
2. Middle East respiratory syndrome coronavirus (MERS-CoV) – The Kingdom of Saudi Arabia. Available at: https://www.who.int/csr/don/24-february-2020-mers-saudi-arabia/en/
3. WHO Coronavirus Disease (COVID-19) Dashboard. Available at: https://covid19.who.int/
4. Bedford J, Enria D, Giesecke J, et al. COVID-19: towards controlling of a pandemic. *Lancet*. 2020;395:1015-1018.
5. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8:e21.
6. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? *J Hypertens*. 2020;38:781-782.
7. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720.

8. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA*. 2020;323:1775-1776.
9. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. *N Engl J Med*. 2020;382:e102.
10. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet*. 2017;389:37-55.
11. Richardson S, Hirsch JS, Narasimhan M, el al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020;323:2052-2059.
12. Sparks MA, Crowley SD, Gurley SB, Mirotsou M, Coffman TM. Classical renin- angiotensin system in kidney physiology. *Compr Physiol*. 2014;4:1201-1228.
13. Ferrario CM, Trask AJ, Jessup JA. Advances in biochemical and functional roles of angiotensin-converting enzyme 2 and angiotensin-(1-7) in regulation of cardiovascular function. *Am J Physiol Heart Circ Physiol*. 2005;289:H2281-2290.
14. Wang K, Gheblawi M, Oudit GY. Angiotensin Converting Enzyme 2: A Double-Edged Sword. *Circulation*. 2020. [Epub ahead of print]
15. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020;181:271-280.
16. Matsuyama S, Nagata N, Shirato K, Kuwase M, Takeda M, Taguchi F. Efficient activation of the severe acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. *J Virol*. 2010;84:12658-12660.
17. Bertram S, Heurich A, Lavender H, et al. Influenza and SARS-coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts. *PLoSOne*. 2012;7:e35876.
18. South, AM, Tomlinson L, Edmonston D, Hiremath S, Sparks MA. Controversies of renin-angiotensin system inhibition during the COVID-19 pandemic. *Nat Rev Nephrol*. 2020;16:305-307.
19. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11:875-876.
20. Ocaranza MP, Godoy I, Jalil JE. Enalapril Attenuates Downregulation of Angiotensin-Converting Enzyme 2 in the Late Phase of Ventricular Dysfunction in Myocardial Infarcted Rat. *Hypertension*. 2006;48:572-578.
21. Deshotels MR, Xia H, Sriramula S, Lazartigues E, Filipeanu CM. Angiotensin II Mediates Angiotensin Converting Enzyme Type 2 Internalization and Degradation Through an Angiotensin II Type I Receptor-Dependent Mechanism. *Hypertension*. 2014;64:1368-1375.
22. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*. 2005;436:112-116.
23. Crackower M, Sarao R, Oudit GY, et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature*. 2002;417:822-828.
24. Huentelman MJ, Grobe JL, Vazquez J. Protection from angiotensin II-induced cardiac hypertrophy and fibrosis by systemic lentiviral delivery of ACE2 in rats. *Exp Physiol*. 2005;90:783-790.
25. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension*. 2004;43:970- 976.
26. Luque M, Martin P, Martell N, Fernandez C, Brosnihan KB, Ferrario CM. Effects of captopril related to increased levels of prostacyclin and angiotensin-(1-7) in essential hypertension. *J Hypertens*. 1996;14:799-805.
27. Arendse LB, Danser AHJ, Poglitsch M, et al. Novel therapeutic approaches targeting the renin–angiotensin system and associated peptides in hypertension and heart failure. *Pharmacol Rev*. 2019;71:539-570.
28. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril insensitive carboxypeptidase. *J Biol Chem*. 2000;275:33238-33243.
29. Mortensen EM, Pugh MJ, Copeland LA, et al. Impact of statins and angiotensin-converting enzyme inhibitors on mortality of subjects hospitalised with pneumonia. *Eur Resp J*. 2008;31:611-617.
30. Christopher H, Manaf Z, Stock E, Ghamande S, Arroliga AC, White HD. Impact of angiotensin-converting enzyme inhibitors and statins on viral pneumonia. *Baylor University Medical Center Proceedings*. 2018;31:419-423.
31. Yang G, Tan Z, Zhou L, et al. Angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors usage is associated with improved inflammatory status and clinical outcomes in COVID-19 patients with hypertension. *medRxiv*. 2020. [Epub ahead of print]
32. Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *EmergMicrob Infect*. 2020;9:757-760.
33. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *N Engl J Med*. 2020;NEJMoa2006923.
34. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. *N Engl J Med*. 2020;NEJMoa2008975.
35. Mehta M, Kalra A, Nowacki AS, et al. Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;e210855.
36. de Abajo FJ, Rodriguez-Martin S, Lerma V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case population study. *Lancet*. 2020;395:1705-1714.
37. Khera R, Clark C, Lu Y, et al. Association of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with the risk of hospitalization and death in hypertensive patients with Coronavirus Disease-19. *medRxiv*. 2020;20104943.
38. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;e200950.
39. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323:1061-1069.
40. European Society of Cardiology. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. 13 Mar 2020. Available at: https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang
41. American Heart Association. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. Available at: https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19.

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