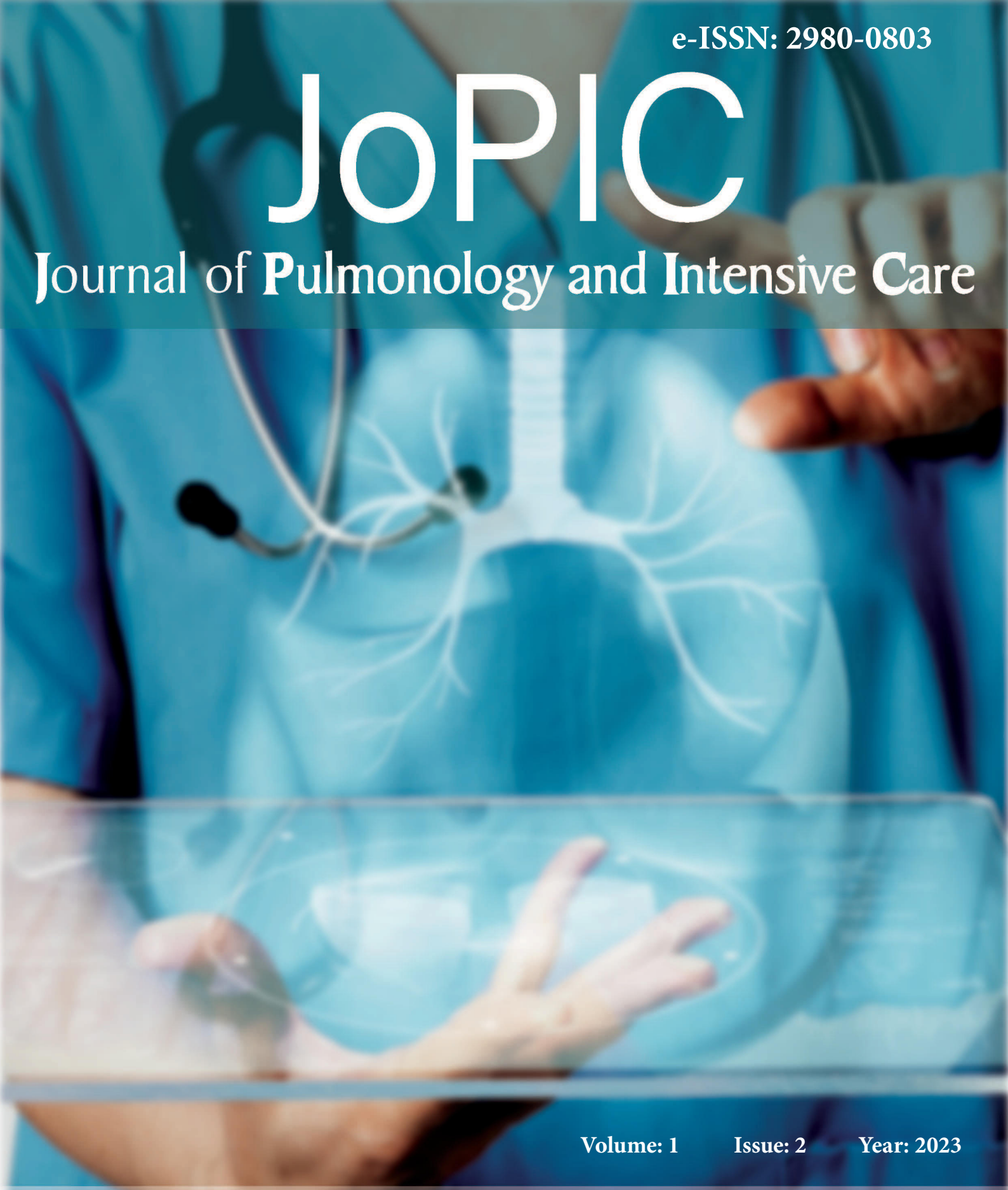
e-ISSN: 2980-0803

JoPIC

Journal of Pulmonology and Intensive Care



Volume: 1 Issue: 2 Year: 2023

MHA
MEDIHEALTH ACADEMY

Journal of
Pulmonology and
Intensive Care

EDITORIAL BOARD

EDITOR-IN-CHIEF

ASSOCIATE EDITORS-IN-CHIEF

EDITORS

EDITORIAL BOARD

Journal of
Pulmonology and
Intensive Care

EDITORIAL BOARD

EDITORIAL BOARD

Journal of
Pulmonology and
Intensive Care

EDITORIAL BOARD

Journal of
Pulmonology and
Intensive Care

EDITORIAL

Dear Colleagues,

As of May 2023, we have published the second issue of Journal of Pulmonology and Intensive Care (JoPIC) under the shield of Medihealth Academy. In addition to all researchers, referees and editorial board who contributed to the preparation of the journal; we would like to thank the printing team for their effort in preparing it for publication. Our main purpose in realizing the idea of this journal is to create a new platform for resarch that we believe will contribute to the literature in the fields of Chest Diseases and Intensive Care, as well as to increase the motivation of researchers with fast and effective article evaluation and publication processes. This second issue includes three original research, two review articles and two case reports. Periodicals are popular with their readers and researchers. In the upcoming period, with your support, our goal is for JoPIC to be indexed in nationally and internationally accepted scientific indexes. I would like to thank you in advance for your contribution.

Assoc. Prof. Berna AKINCI ÖZYÜREK, MD
Editor in Chief

Journal of
Pulmonology and
Intensive Care

CONTENTS

Volume: 1 Issue: 2 Year: 2023

ORIGINAL ARTICLE

REVIEW

CASE REPORT

Journal of
Pulmonology and
Intensive Care

Original Article

DOI: 10.51271/JOPIC-0005

The effect of deep and superficial serratus anterior plane block on postoperative acute pain for thoracoscopic surgery patients; a prospective randomized trial

Musa Zengin[1], Hilal Sazak[2], Oya Kaybal[2], Ramazan Baldemir[2], Gülay Ulger[2], Dilara Arıcan[2], Ali Alagöz[2]

[1]Department of Anesthesiology and Reanimation, Ankara Etlik City Hospital, Ankara, Turkey
[2]Department of Anesthesiology and Reanimation, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkey

Cite this article: Zengin M, Sazak H, Kaybal O, et al. The effect of deep and superficial serratus anterior plane block on postoperative acute pain for thoracoscopic surgery patients; a prospective randomized trial. *J Pulmonol Intens Care.* 2023;1(2):23-27.

Corresponding Author: Musa Zengin, musazengin@gmail.com

Received: 28/03/2023 ◆ **Accepted**: 04/05/2023 ◆ **Published**: 22/05/2023

ABSTRACT

Aims: In recent years, video-assisted thoracoscopic surgery (VATS) is increasingly preferred over open thoracotomy. Serratus anterior plane block (SAPB) is the preferred analgesic technique in VATS interventions. This study, it was aimed to compare the postoperative analgesic efficacy of superficial SAPB (SSAPB) and deep SAPB (DSAPB) in patients undergoing lung resection with VATS.

Methods: The study was conducted with a prospective, randomized, single-blind design. The ethics committee approval was obtained for the study. The patients, in the age range of 18 to 65 years, with the American Society of Anesthesiologists (ASA) physical status of I-III, and body mass index (BMI) of 18-30 kg/m², and undergoing lung resection with VATS were included in the study. Patients were informed about the study, and their written consent was obtained. Patients were assigned to DSAPB (Group 1) and SSAPB (Group 2) groups according to the analgesia protocol.

Results: After obtaining ethical committee approval, 60 patients were included in the study. Eight patients who converted from VATS to thoracotomy were excluded from the study. There was no statistically significant difference between the groups in terms of demographic characteristics, surgical features, side effects, morphine consumption, and additional analgesic use ($p>0.05$). When the groups were evaluated in terms of the duration of the block procedure, it was found to be statistically significantly longer in the SSAPB group than in the DSAPB group ($p<0.001$).

Conclusion: Both DSAPB and SSAPB were effective and had similar analgesic actions. The shorter block procedure time in DSAPB may be an advantage when considering similar analgesic effects.

Keywords: Acute pain, deep serratus anterior plane block, superficial serratus anterior plane block, video-assisted thoracoscopic surgery.

INTRODUCTION

In recent years, video-assisted thoracoscopic surgery (VATS) is increasingly preferred over open thoracotomy. The popularity of VATS has gradually increased due to the widespread use of applications defined as enhanced recovery after surgery (ERAS), the preference of less invasive surgical techniques, and less associated with postoperative complications.[1,2] Although it is performed via a smaller incision compared to thoracotomy, pain after VATS is still a problem that needs to be resolved. Postoperative severe pain; by making it difficult for the patient to cough, it may cause accumulation of secretions, decrease in functional residual capacity and, as a result, increase in morbidity.[3] Since the formation of postoperative pain depends on tissue damage, preemptive analgesia applications remain on the agenda in the treatment of pain.[4] Although the application of thoracic epidural analgesia (TEA) is considered the gold standard for the treatment of pain in thoracic surgery, in recent years, considering the serious complications associated with TEA application, regional interfacial nerve blocks under ultrasound (US) guidance have been preferred.[5,6] Nowadays, erector spinae plane block (ESPB) and serratus anterior plane block (SAPB) are the most preferred techniques in VATS interventions. The application of such regional blocks is technically easier than TEA or even thoracic paravertebral block (TPVB) and is supported by ERAS protocols besides having lower complication rates.[7]

SAPB is a new technique that provides an analgesic effect by blocking the lateral branch of the intercostal nerve.[8] This block has become a popular analgesic modality as it is easy to administer and relatively safe.[8,9] SABP has two different methods as a deep and superficial application.[8-10] While blocking is applied to the plane between the latissimus dorsi and serratus anterior muscles in superficial SABP (SSAPB); it is applied to the deep plane between the serratus anterior muscle and the rib/external intercostal muscle in deep SABP (DSAPB).[8-10] There are still controversial results about the superiority of these blocks. In VATS applications, publications are showing that SSAPB has a longer and wider blockage area than DSAPB, and there are also publications in the literature showing that these two methods are not superior to each other.[8-10]

We hypothesized that SAPB may be effective in reducing postoperative pain in patients undergoing VATS and that SSAPB or DSAPB methods may exhibit different properties. It was aimed to compare the postoperative analgesic efficacy and application times of SSAPB and DSAPB in patients undergoing lung resection with VATS. The VAS pain scores during the first 48 hours after surgery were determined as the primary outcome. The 24-hour morphine consumption, additional analgesic requirements, and block performance time were of the patients were determined as the secondary outcome.

METHODS

The randomized and prospective trial was conducted in a high-volume tertiary thoracic surgery center after obtaining approval from Ankara City Hospital Ethics Committee (Date: 22.10.2021, Decision No: E1-21-2067). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The patients, in the age range of 18 to 65 years, with the American Society of Anesthesiologists (ASA) physical status of I-III, and body mass index (BMI) of 18-30 kg/m², and undergoing lung resection with VATS were included in the study. Patients were informed about the study, and their written consent was obtained.

During the preoperative evaluation, the patients were informed about pain assessment and patient-controlled analgesia (PCA). Patients with preoperative acute or chronic pain and a history of opioid therapy were excluded. Moreover, patients with bleeding disorders, infection at the injection site, or allergy to local anesthetics, and patients who underwent emergency surgery were excluded from the study. In addition, patients who converted from VATS to thoracotomy were also excluded from the study.

Patients were divided into DSAPB (Group 1) and SSAPB (Group 2) groups according to the analgesia protocol. Randomization was achieved with computer-generated random numbers.

Patients were monitored in the operating room following the ASA standards. Patients were administered 0.03 mg/kg midazolam for premedication. Following preoxygenation, anesthesia was induced with 2 mg/kg propofol, 1 mcg/kg fentanyl, and 0.1 mg/kg vecuronium. After intubation with a left-sided double-lumen endobronchial tube, tube localization was confirmed. Anesthesia was maintained with sevoflurane in a mixture of oxygen and air. Additionally, remifentanil infusion at a dose of 0.01-0.20 mcg/kg/min was administered.

Block procedures were performed under general anesthesia before the skin incision to prevent anxiety and ensure patient comfort. Following the anesthesia induction, blocks were performed under US guidance when patients were in the lateral decubitus position. After strict skin antisepsis, the needle insertion area was covered with sterile drapes. A high-frequency 6–18 MHz linear probe (MyLab six, Esaote, Genoa, Italy) in a sterile cover and a US-compatible 22-gauge and 8-mm nerve block needle (Pajunk, SonoPlexSTIM, Germany) were used in all groups. Block performance times were noted based on the entry of the block needle into the skin and the exit of the needle after the block. The following procedures were performed in the study groups:

DSAPB group (n:30): Following the visualization of the anatomical structures, the nerve block needle was advanced via the in-plane technique until reaching the fourth rib. Hydrodissection with 2 ml of normal saline was performed beneath the serratus anterior muscle, and a volume of 20 ml of 0.25% bupivacaine was injected into the area (**Figure 1**).

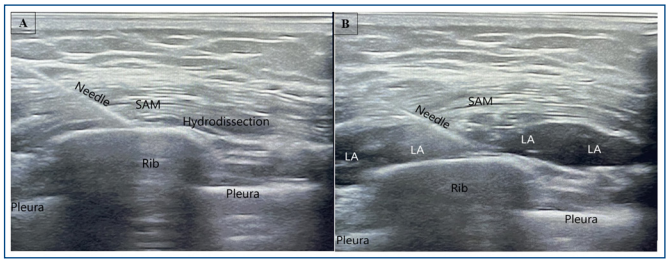


Figure 1. Deep serratus anterior plan block procedure. A: Anatomical scene before the block and hydrodissection with 2 ml of saline solution was performed into the interfascial plane above the rib and below the SAM. B: Deep serratus anterior plan block; The local anesthetic spread beneath the serratus anterior muscle. SAM: serratus anterior muscle, LA: local anesthetic.

SSAPB group (n: 30): After the visualization of the anatomical structures, the needle was advanced via the in-plane technique above the serratus anterior muscle; hydro dissection with 2 ml of normal saline was performed in the interfascial space, and a volume of 20 ml of 0.25% bupivacaine was injected into the area (**Figure 2**).

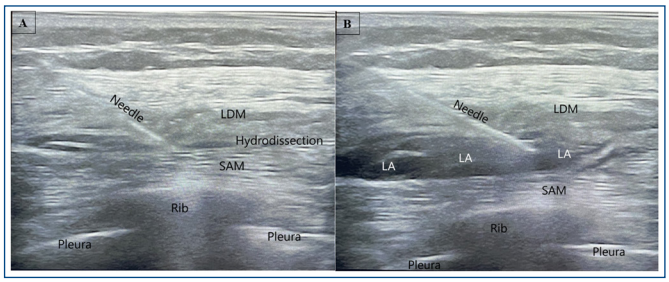


Figure 2: Superficial serratus anterior plan block procedure. A: Anatomical scene before the block and hydrodissection with 2 ml of saline solution was performed into the interfascial plane above the SAM and below the LDM. B: Superficial serratus anterior plan block; The local anesthetic spread above the serratus anterior muscle. LA: local anesthetic, LDM: Latissimus Dorsi Muscle, SAM: serratus anterior muscle.

During the skin closure, patients received dexketoprofen and tramadol intravenously. Metoclopramide was administered intravenously to avoid nausea and vomiting. In the postoperative surgical intensive care unit, intravenous morphine was administered via PCA pump for 24 hours. Pain intensity was evaluated using a 10- point (0: No pain and 10: Unbearable pain) visual analog scale (VAS). The PCA pump's dose delivery was limited to administering a

bolus dose of 1 mg morphine and delivering a maximum dose of 12 mg morphine in total within 4 hours with lockout intervals of 15 minutes. Paracetamol 1 g every 8 hours and dexketoprofen 50 mg twice daily were administered intravenously for multimodal analgesia. As a rescue analgesic agent, 0.5 mg/kg tramadol was given to patients intravenously when a score of VAS at rest was ≥4. The patients were transferred to the ward in the postoperative 24th hour. Paracetamol 500 mg tablets and tramadol 50 mg capsules every 8 hours and dexketoprofen 25 mg tablets every 12 hours were given after the postoperative second day. VAS scores at rest and while coughing were recorded in the postoperative 1st hour, 2nd hour, 4th hour, 8th hour, 16th hour, 24th hour, and 48th hour. The need for additional analgesics and side effects including allergic reactions, respiratory depression, sedation, hypotension, urinary retention, nausea-vomiting, and itching were recorded. In two groups, patients' hemodynamic data, age, BMI, gender, diagnosis, the type of surgery, intraoperative and postoperative complications, postoperative VAS scores, and postoperative additional analgesic use were recorded. The block was applied to all patients by the same attending anesthesiologist. The VAS score was followed up by the pain management nurse who was blinded to the type of block applied to the patient. All VATS procedures were applied by the same surgical team with sufficient experience in this regard in the third-level thoracic surgery center. A single polyvinylchloride chest tube was introduced, made of two openings, a camera port, and a utility.

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by the Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean ± SD for normal distributions, and median (interquartile range). for skewed distributions. Categorical data were described as a number of cases (%). Statistical analysis differences in normally distributed variables between two independent groups were compared by Student's t-test, Mann Whitney U test was applied for comparisons of the not normally distributed data. Categorical variables were compared using Pearson's chi-square test or fisher's exact test was accepted p-value <0.05 as a significant level on all statistical analysis.

The sample size was calculated using G*Power© software version 3.1.9.2 (Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany). The sample size was calculated for the mann whitney u-test, which was used for testing the main hypothesis of (VAS scores at rest in the first postoperative hour) the present study. Depending on previous research results with two-sided (two tails) type I error 0.05 and power of 80% (1-β=0.8), effect size (d) factor 0.88, should involve ≥ 44 subject.

RESULTS

After obtaining ethical committee approval, 60 patients were included in the study. Eight patients who converted from VATS to thoracotomy were excluded from the study. (**Figure 3**).

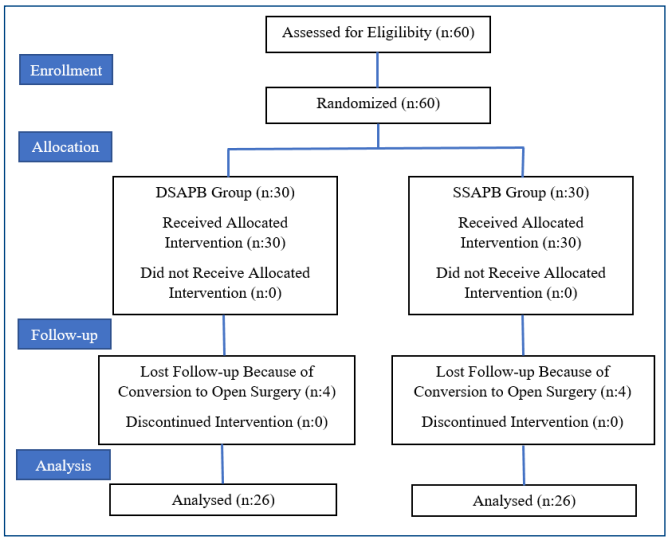


Figure 3: Flow Chart. DSAPB: Deep Serratus Anterior Plane Block, SSAPB: Superficial Serratus Anterior Plane Block

There was no statistically significant difference between the groups in terms of demographic characteristics, surgical features, side effects, morphine consumption, and additional analgesic use (p>0.05) (**Table 1**).

Table 1: Demographic characteristics, surgical features, side effects, remifentanil consumption, morphine consumption, additional analgesic use, duration of the block procedure of the patients.

	DSAPB (n:26)	SSAPB (n:26)	p
Age (year)	51.5 (15)	53.5 (19)	0.905$^{\beta}$
Gender			0.999$^{\delta}$
Female	7 (26.9%)	7 (26.9%)	
Male	19 (73.1%)	19 (73.1%)	
BMI	25.7 (6.5)	24.45 (5.9)	0.458$^{\beta}$
Operation			0.999$^{\delta}$
Wedge	23 (88.5%)	23 (88.5%)	
Lobectomy	3 (11.5%)	3 (11.5%)	
Duration of operation (minute)	180 (60)	150(60)	0.599$^{\beta}$
Block performance time (second)	118.19 ± 11.92	134,65±8,63	<0.001*
ASA			0.578$^{\delta}$
ASA II	13 (50.0%)	15 (57.7%)	
ASA III	13 (50.0%)	11 (42.3%)	
Nausea, Yes	4 (15.4%)	3 (11.5%)	0.999$^{\delta}$
Additional analgesic use, Yes	9 (34.6%)	6 (23.1%)	0.358$^{\delta}$
Intraoperative remifentanil consumption (mcg)	420.00±175.45	411.15±141.29	0.842*
Morphine consumption (mg)	21.35±12.87	18.62±10.89	0.413*

Continuous variables are expressed as either * the mean ± standard deviation (SD) or β the median ((interquartile range), and categorical variables are expressed as either δ frequency or percentage. Continuous variables were compared with an student T Test or the Mann Whitney U Test, and categorical variables were compared using Pearson's Chi-Square Test or Fisher Exact Test. Statistically significant p-values are in bold. BMI: Body mass index. ASA: American Society of Anesthesiologist.

When the groups were evaluated in terms of the block performance time, it was found to be statistically significantly longer in the SSAPB group than in the DSAPB group (p< 0.001) (**Table 1**).

No statistically significant difference was observed between the groups in terms of hemodynamic parameters and SpO_2 (p >0.05).

There was no statistically significant difference between the groups in terms of all VAS resting and VAS coughing (p>0.05) (**Figure 4**) (**Table 2**).

Table 2: Resting and coughing VAS scores during the postoperative 48 hours.

	DSAPB (n:26)	SSAPB (n:26)	p
	Med (IQR)	Med (IQR)	
VAS at rest			
1st hour	3 (2)	3 (1)	0.430
2nd hour	2,5 (2)	2 (1)	0.726
4th hour	2 (2)	2 (2)	0.832
8th hour	2 (2)	2 (1)	0.977
16th hour	1 (1)	1 (1)	0.530
24th hour	1 (1)	1 (2)	0.520
48th hour	2 (2)	2 (2)	0.748
VAS at cough			
1st hour	4 (2)	4 (2)	0.468
2nd hour	4 (2)	3 (2)	0.748
4th hour	3 (2)	3 (2)	0.895
8th hour	3 (2)	3 (1)	0.682
16th hour	2 (1)	2.5 (1)	0.938
24th hour	2 (1)	2 (2)	0.621
48th hour	3 (1)	3 (2)	0.621

Continuous variables are expressed as the median (interquartile range). Continuous variables were compared with the Mann-Whitney U test. Statistically significant p-values are in bold.

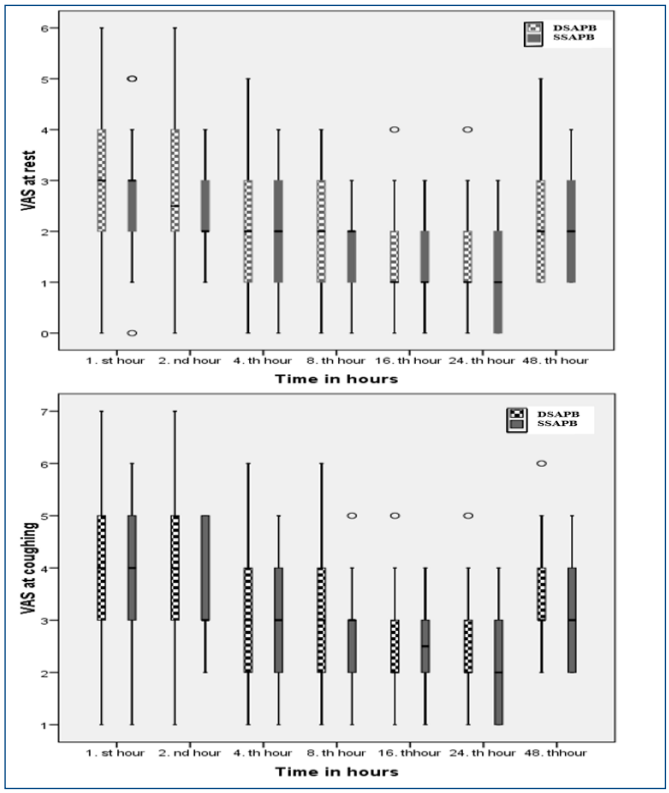


Figure 4: VAS scores at rest and VAS scores at coughing. Data are expressed as median (horizontal bars), interquartile range (boxes), and maximum and minimum values (whiskers) for the VAS scores in the 1st, 2nd, 4th, 8th, 16th, 24th hours, and 48th hours. DSAPB: Deep Serratus Anterior Plane Block, SSAPB: Superficial Serratus Anterior Plane Block, VAS: Visual analog scale.

DISCUSSION

The results of this study showed that both DSAPB and SSAPB provided effective postoperative analgesia in patients who underwent VATS. Although their analgesic effects are similar, the shorter block performance time in DSAPB can be considered as an advantage of this practice.

In recent years, VATS has become an increasingly preferred method in lung resections because it is a less invasive treatment method.[1] Although the pain is more limited compared to thoracotomy, severe pain may be encountered, especially in the first 24 hours postoperatively, and this may last longer.[3,8] Poorly controlled postoperative pain may limit the patient's effective coughing function, resulting in pulmonary infections and delayed recovery.[3] Various analgesic methods are used to relieve pain after VATS, techniques such as TPVB, ESPB, SSAPP, and DSAPB have been increasingly used recently.[7] These applications are also one of the most important elements of multimodal analgesia, which is a component of ERAS protocols, the main concept of which aims to accelerate the surgical process with the least invasive intervention possible.[7] In addition, TPVB, ESPB, and SAPB have recently been recommended by the European Society of Regional Anaesthesia (ESRA) as methods of choice for postoperative analgesia after VATS (recommendation grade: A, for all 3 techniques).[11] SAPB application seems to be more practical and safe due to the relative difficulty of TPVB and ESPB application, and the proximity to the pleura and vascular structures, especially in TPVB. In addition, studies have revealed that similar results in terms of postoperative analgesia are obtained with TPVB and ESPB in SAPB applications. Anatomically, the serratus anterior muscle originates on the surface of the first 8 ribs and attaches to the medial border of the scapula and posterior aspect of the latissimus dorsi. Intercostal nerves pierce the muscle and pass through the deep and anterior planes of the serratus anterior muscle in transition to the subcutaneous tissue.[12] This anatomical location may provide adequate analgesia effect at T2 to T9 levels in patients undergoing SAPB. Another advantage of SAPB applications is that they are easier to view and easier to implement than TPVB and ESPB.[8]

Studies comparing the analgesic efficacy of DSAPB and SSAPB after VATS are very limited.[8-10] Blanco et al.[9] argued that SSAPB has a wider block area in their study. While Piracha et al.[13] found that DSAPB could offer better analgesia compared to superficial injection in four patients undergoing breast surgery, Abdallah et al.[14] found similar analgesic effects with both plane blocks after breast surgery. On the other hand, a study by Qui et al.[8] showed that superficial SAPB is more effective. The widespread use of local anesthesia in the deep or superficial block is still controversial. Biswas et al.[15] in a cadaver study, with a high-volume injection technique, provided widespread and consistent dye distribution in the anterior chest wall and axilla, regardless of superficial or deep application. However, they stated that its distribution in the posterior area is more limited. Qui et al.[8] showed in their study that SSAPB creates a more effective block compared to DSAPB. The authors argued that this situation may be related to complete or partial blockage of the long thoracic nerve innervating the serratus anterior muscle with SSAPB. It was evaluated as this blockade provided more effective analgesia by blocking the anterior branches of the intercostal nerves. In this study, we observed similar analgesic actions with both SSAPB and DSAPB in the postoperative 48-hour period.

There is no consensus on the ideal local anesthetic injection volume for SAPB. Major studies on this subject are at the level of cadaver or imaging studies.[15,16] Kunigo et al.[17] compared SAPB applications using 20 mL and 40 mL of ropivacaine for postoperative analgesia after breast cancer surgery and found that higher volume produced a better analgesic effect and that the blocking effect could be sufficient and safer with lower doses also. In this study where we kept the local anesthetic volume constant at 20 ml, we achieved sufficient analgesic effect.

Block performance times are important in terms of showing the easy applicability of the block. This is important not only for limiting the time spent on the block but also for the convenience of the process. In studies on SAPB applications, the block procedure duration has not come to the fore.[8-14] However, Edwards et al.[18] evaluated DSAPB and SSAPB in terms of the duration of the block procedure in patients who underwent breast surgery and found the duration of block application to be shorter in patients who underwent DSAPB. In our study, the DSAPB application was completed in a shorter time than the superficial application. This can be explained by the rapid acquisition of the ultrasound image due to the rib and the fact that the deep serratus region is less mobile due to its proximity to the rib during application. In addition to providing similar analgesic effects with SSAPB, we think that DSAPB, which can be administered in a shorter time, may be a good alternative to SSAPB. Moreover, we think that since the area where DSAPB is applied is directly above the rib and away from the pleura, it will not pose a problem in terms of safe block application.

Qui et al.[8] found that the number of patients who developed nausea and vomiting in patients who underwent SSAPB was higher without significance after VATS. In this study, we observed only nausea as a side effect in the DSAPB and SSAPB groups. However, although this rate was higher in the SSAPB group, there was no significant difference between the groups. Considering that many factors are effective in the development of PONV after surgery, it may not be possible to evaluate whether the applied blocks may be related to PONV.

The present study has some limitations. The study was conducted at a single center. In the study, the block was applied using the same local anesthetic volumes in both blocks. Studies with different volumes may be useful in evaluating the effect on block quality. In addition, the long-term analgesic effects of these two blocks could not be evaluated in this study.

CONCLUSION

In this study comparing DSAPB and SSAPB in patients who underwent VATS lung resection, safe and effective analgesia was obtained with both blocks. Although their analgesic effects are similar, the shorter block procedure time in DSAPB can be considered as an advantage of this practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 22.10.2021, Decision No: E1-21-2067).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Wu N, Wu L, Qiu C, et al. A comparison of video-assisted thoracoscopic surgery with open thoracotomy for the management of chest trauma:a systematic review and meta-analysis. *World J Surg.* 2015;39(4):940-952. doi:10.1007/s00268-014-2900-9
2. Flores RM, Park BJ, Dycoco J, et al. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. *J Thorac Cardiovasc Surg.* 2009;138(1):11-18. doi:10.1016/j.jtcvs.2009.03.030
3. Łochowski MP, Kozak J. Video-assisted thoracic surgery complications. *Wideochir Inne Tech Maloinwazyjne.* 2014;9(4):495-500. doi:10.5114/wiitm.2014.44250
4. Neustein SM, McCormick PJ. Postoperative analgesia after minimally invasive thoracoscopy: what should we do? *Can J Anaesth.* 2011;58(5):423-427. doi:10.1007/s12630-011-9475-9
5. Loop T. Fast track in thoracic surgery and anaesthesia: update of concepts. *Curr Opin Anaesthesiol.* 2016;29(1):20-5. doi:10.1097/ACO.0000000000000282
6. Hamilton DL, Manickam B. Erector spinae plane block for pain relief in rib fractures. *Br J Anaesth.* 2017;118(3):474-475. doi:10.1093/bja/aex013
7. Kaplowitz J, Papadakos PJ. Acute pain management for video-assisted thoracoscopic surgery:an update. *J CardiothoracVascAnesth.* 2012;26(2):312-321. doi:10.1053/j.jvca.2011.04.010
8. Qiu L, Bu X, Shen J, et al. Observation of the analgesic effect of superficial or deep anterior serratus plane block on patients undergoing thoracoscopic lobectomy. *Medicine (Baltimore).* 2021;100(3):e24352. doi:10.1097/MD.0000000000024352
9. Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block:a novel ultrasound-guided thoracic wall nerve block. *Anaesthesia.* 2013;68(11):1107-13. doi:10.1111/anae.12344
10. Moon S, Lee J, Kim H, Kim J, Kim J, Kim S. Comparison of the intraoperative analgesic efficacy between ultrasound-guided deep and superficial serratus anterior plane block during video-assisted thoracoscopic lobectomy: a prospective randomized clinical trial. *Medicine (Baltimore).* 2020;99(47):e23214. doi:10.1097/MD.0000000000023214
11. Feray S, Lubach J, Joshi GP, Bonnet F, Van de Velde M; PROSPECT Working Group *of the European Society of Regional Anaesthesia and Pain Therapy. PROSPECT guidelines for video-assisted thoracoscopic surgery: a systematic review and procedure-specific postoperative pain management recommendations. *Anaesthesia.* 2022;77(3):311-325. doi:10.1111/anae.15609
12. Willard FH, Vleeming A, Schuenke MD, Danneels L, Schleip R. The thoracolumbar fascia:anatomy, function and clinical considerations. *J Anat.* 2012;221(6):507-536. doi:10.1111/j.1469-7580.2012.01511.x
13. Piracha MM, Thorp SL, Puttanniah V, Gulati A. "A tale of two planes": deep versus superficial serratus plane block for postmastectomy pain syndrome. *Reg Anesth Pain Med.* 2017;42(2):259-262. doi:10.1097/AAP.0000000000000555
14. Abdallah FW, Cil T, MacLean D, et al. Too deep or not too deep?: a propensity-matched comparison of the analgesic effects of a superficial versus deep serratus fascial plane block for ambulatory breast cancer surgery. *RegAnesth Pain Med.* 2018;43(5):480-487. doi:10.1097/AAP.0000000000000768
15. Biswas A, Castanov V, Li Z, et al. Serratus plane block:a cadaveric study to evaluate optimal injectate spread. *RegAnesth Pain Med.* 2018 ov;43(8):854-858. doi:10.1097/AAP.0000000000000848
16. Kunigo T, Murouchi T, Yamamoto S, Yamakage M. Spread of injectate in ultrasound-guided serratus plane block:a cadaveric study. *JA Clin Rep.* 2018;4(1):10. doi:10.1186/s40981-018-0147-4
17. Kunigo T, Murouchi T, Yamamoto S, Yamakage M. Injection volume and anesthetic effect in serratus plane block. *RegAnesth Pain Med.* 2017;42(6):737-740. doi:10.1097/AAP.0000000000000649
18. Edwards JT, Langridge XT, Cheng GS, McBroom MM, Minhajuddin A, Machi AT. Superficial vs. deep serratus anterior plane block for analgesia in patients undergoing mastectomy: a randomized prospective trial. *J Clin Anesth.* 2021;75:110470. doi:10.1016/j.jclinane.2021.110470

Journal of
Pulmonology and
Intensive Care

Original Article

DOI: 10.51271/JOPIC-0006

The evaluation of asthma by gender and age groups in Turkey, in 1990-2019: incidence, prevalence, mortality, and disability-adjusted life years

Metin Dinçer[1], Mustafa Kocakaya[1], Mesut Akyol[2]

[1]Department of Health Management, Faculty of Health Sciences, Ankara Yıldırım Beyazıt University, Ankara, Turkey
[2]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Turkey

Cite this article: Dinçer M, Kocakaya M, Akyol M. The evaluation of asthma by gender and age groups in Turkey, in 1990-2019: incidence, prevalence, mortality, and disability-adjusted life years. *J Pulmonol Intens Care.* 2023;1(2):28-31.

Corresponding Author: Mustafa Kocakaya, mustafakocakaya7@gmail.com

Received: 28/04/2023 ◆ **Accepted**: 02/05/2023 ◆ **Published**: 22/05/2023

ABSTRACT

Aims: The aim of this study was to evaluate the incidence and prevalence of asthma, asthma-related DALYs and deaths, and risk factors for asthma by genders and age groups during the study years in Turkey.

Methods: The data used in the study were obtained from the estimation data prepared by the Institute for Health Metrics and Evaluation on asthma for Turkey by the global burden of disease study covering the years 1990-2019. During the study years period, death from asthma and Disability-Adjusted Life Years (DALYs) were used as dependent variables. In addition, the effects of Occupational Asthmagens (OA), Smoking (SM), and High Body Mass Index (HBMI), which are known as risk factors for asthma-related deaths and DALYs, were investigated. Comparisons of the variables according to gender and age groups were made with the Mann-Whitney test. The relationships between the variables were examined with the Spearman rank correlation coefficient (Rho).

Results: A statistically significant difference was found between the mean rank of total prevalence number, total incidence number, total number of deaths and DALYs scores by gender. Asthma-related deaths due to risk factors (OA, HBMI, SM) were found to be correlated with DALYs and the total number of asthma deaths. Total asthma deaths, and asthma-related deaths because of HBMI and DALYs because of HBMI-induced asthma in women; deaths from asthma because of OA, SM, and DALYs from asthma because of OA and SM were found to be higher in males.

Conclusion: HBMI in women and SM and OA in men stand out as risk factors. Therefore, as a result of a detailed investigation of the risk factors leading to the development of asthma, policies should be developed for gender and age groups, and necessary precautions should be taken.

Keywords: Asthma deaths, DALY, prevalence, incidence, risk factors

INTRODUCTION

Asthma; is a chronic lung disease that can cause structural and functional changes, causing symptoms such as recurrent wheezing, coughing, shortness of breath, and chest tightness.[1] Asthma is an important non-communicable disease affecting both children and adults.[2] Asthma is estimated to affect 262 million people worldwide[3] and cause 455 thousand deaths in 2019.[2]

Factors such as allergens (dust, mold, pet hair, etc.), environmental factors (air pollution, chemicals, etc.), genetic and behavioral factors (smoking, high body mass index -obesity- etc.) cause asthma and the disease for those with existing disease. increases the severity.[4-8] Smoking causes disease through both direct use and exposure to smoke.[8] Occupational asthma occurs when the person is exposed to the factors that cause the disease in the working environment.[4]

One Disability-Adjusted Life Year (DALY) represents a loss equivalent to one year of complete health loss.[9] It is also equal to the sum of the number of healthy years lost because of mortality and morbidity.[10] DALYs are included in the study because they include years of healthy life lost not only because of death but also because of disease. In this study, asthma incidence, prevalence, asthma-related DALYs and deaths, and risk factors causing asthma in Turkey will be evaluated according to gender and age groups during the study years.

METHODS

Since public data was used in this study, there is no need for an ethics committee decision. All transactions were carried out in accordance with ethical rules and principles. In the study, it was obtained from the estimation data prepared

by the Institute for Health Metrics and Evaluation (IHME-healthdata.org) on asthma disease for Turkey in the global disease burden study covering the years 1990-2019.[11] The variables investigated in the study include asthma-related deaths, asthma-induced DALYs, asthma incidence, and asthma prevalence. Asthma-related deaths and DALYs have been associated with three different risk factors; Occupational asthmagens (OA), Smoking (SM), and High Body Mass Index (HBMI). A risk factor is a condition that causes disease in people who carry it, resulting in death or disability.[12] The death and DALY variables used in the study and caused by risk Factors are as follows: (1) OA-induced asthma-related deaths (OAD), (2) SM-induced asthma-related deaths (SMD), (3) HBMI-induced asthma-related deaths (HBMID). (4) OA-induced asthma-induced DALYs (OADALYs), (5) SM-induced asthma-induced DALYs (SMDALYs), and (6) HBMI-induced asthma-induced DALYs (HBMIDALYs). The selection of risk factors could be made according to the availability of data in IHME.

For each of the variables described above, the number (number of deaths in the population), percent (proportion of deaths from a specific cause compared to deaths from all causes), and rate (deaths per 100,000 population) values were obtained. Each of the variables used in the study was evaluated according to gender (female, male, and all genders together) and age groups. Since data can be obtained in the range of 1-95+ years for HBMI, 30-95+ years for SM and 15-84 years for OA, age groups are arranged accordingly and evaluated as 5-year age groups at the specified intervals.

Within the scope of the research, the conformity of the number, percent, and rate values collected for death and DALYs to the normal distribution was examined graphically and using the Shapiro-Wilk test. It was determined that the values of all the variables examined were skewed and did not comply with the normal distribution. All descriptive statistics are given as median (IQR: Inter Quartile Range). Comparisons by gender were made using the Mann-Whitney test. The relationships between the variables used in the study were examined with the Spearman rank correlation coefficient (Rho).

Ms-Excel 2016 and IBM SPSS Statistics 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, IBM Corp.) programs were used for statistical analysis, calculations, and graphic drawing. In statistical decisions, $p<0.05$ was accepted as an indicator of a significant difference.

RESULTS

Total asthma-related deaths (**Figure 1-a**), deaths due to risk factors causing asthma (**Figure 1-b, c, d**), and DALYs caused by risk factors (**Figure 1-f, g, e**) are presented graphically.

It is shown that the total number of asthma deaths, HBMID and HBMIDALYs were higher in women; OAD, SMD, OADALYs, and SMDALYs were higher in men. When evaluated by years, there was an increase in HBMID and HBMIDALYs, while death because of other factors and a decrease in DALYs (only DALYs because of smoking increased slightly in women).

A statistically significant relationship ($p<0.001$) was found between the total number of asthma-related deaths and three asthma risk factors for all age groups. While a very strong relationship was found between the total number of deaths from asthma and HBMI in all age groups, a strong relationship was also found between OAD and SMD. The relationship between the total number of deaths from asthma, OAD, and SMD decreases with increasing age (**Table 1**).

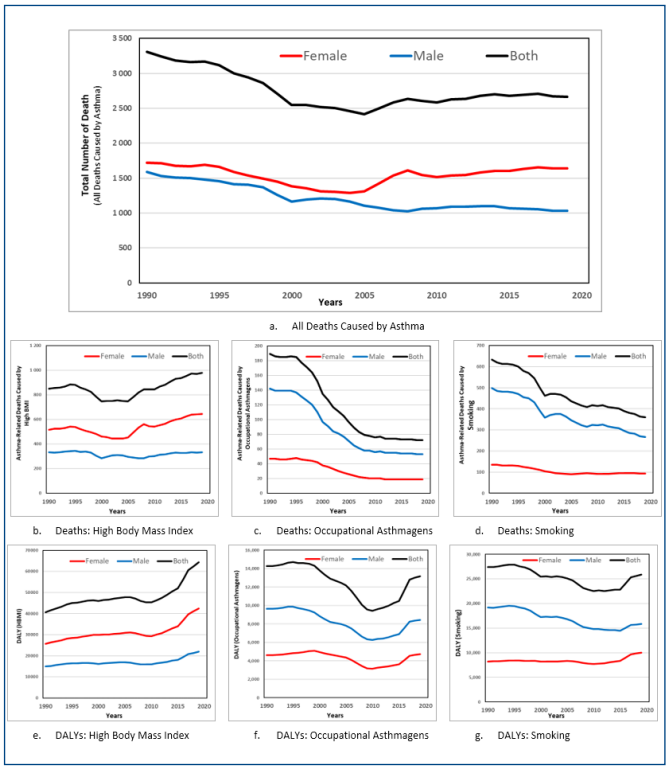


Figure 1. Number of Asthma-related deaths and DALY's by gender and year

Table 1. Relationships between total number of deaths and risk factors for all age groups (years)

Age_Grup (Years-Deaths*)	HBMID**		OAD***		SMD****	
	Rho	p	Rho	p	Rho	
1-4	0.991	<0.001	–	–	–	–
5-9	0.995	<0.001	–	–	–	–
10-14	0.977	<0.001	–	–	–	–
15-19	0.976	<0.001	0.971	<0.001	–	–
20-24	0.981	<0.001	0.937	<0.001	–	–
25-29	0.979	<0.001	0.823	<0.001	–	–
30-34	0.973	<0.001	0.780	<0.001	0.813	<0.001
35-39	0.975	<0.001	0.761	<0.001	0.844	<0.001
40-44	0.967	<0.001	0.663	<0.001	0.702	<0.001
45-49	0.945	<0.001	0.750	<0.001	0.813	<0.001
50-54	0.943	<0.001	0.810	<0.001	0.804	<0.001
55-59	0.910	<0.001	0.868	<0.001	0.836	<0.001
60-64	0.893	<0.001	0.827	<0.001	0.832	<0.001
65-69	0.948	<0.001	0.668	<0.001	0.655	<0.001
70-74	0.875	<0.001	0.598	<0.001	0.629	<0.001
75-79	0.965	<0.001	0.350	0.001	0.519	<0.001
80-84	0.982	<0.001	0.402	<0.001	0.451	<0.001
85-89	0.983	<0.001	–	–	0.402	<0.001
90-94	0.961	<0.001	–	–	0.435	<0.001
95+	0.982	<0.001	–	–	0.269	0.010

*Number: Number of deaths in the population.
**OAD: Number of asthma-related deaths caused by Occupational Asthmagens
***SMD: Number of asthma-related deaths caused by Smoking
****HBMID: Number of deaths from asthma caused by High Body Mass Index

When the relationships between the number of asthma deaths due to risk factors were analyzed according to age groups, a significant relationship was found between HBMID and OAD for all age groups, except for the 75 and over age group ($p<0.05$). On the other hand, there was a significant relationship between

HBMID and SMD in all age groups (p<0.05), except for the 95-year-old and older group, but the strength of the relationship decreased as age increased. A very strong correlation was found between OAD and SMD in the same direction for each group between the ages of 30-84 (p<0.001) (**Table 2**).

Table 2. Relationships between risk factors for all age groups (years)

Age_Grup (years-number*)	HBMID**-OAD***		HBMID-SMD****		SMD-OAD	
	Rho	p	Rho	p	Rho	p
15-19 years	0.969	<0.001	–	–	–	–
20-24 years	0.943	<0.001	–	–	–	–
25-29 years	0.770	<0.001	–	–	–	–
30-34 years	0.672	<0.001	0.709	<0.001	0.996	<0.001
35-39 years	0.668	<0.001	0.755	<0.001	0.981	<0.001
40-44 years	0.509	<0.001	0.543	<0.001	0.990	<0.001
45-49 years	0.585	<0.001	0.656	<0.001	0.989	<0.001
50-54 years	0.639	<0.001	0.635	<0.001	0.990	<0.001
55-59 years	0.666	<0.001	0.611	<0.001	0.991	<0.001
60-64 years	0.579	<0.001	0.567	<0.001	0.986	<0.001
65-69 years	0.454	<0.001	0.443	<0.001	0.985	<0.001
70-74 years	0.261	0.013	0.294	0.005	0.990	<0.001
75-79 years	0.193	0.069	0.343	0.001	0.841	<0.001
80-84 years	0.273	0.009	0.332	0.001	0.834	<0.001
85-89 years	–	–	0.301	0.004	–	–
90-94 years	–	–	0.276	0.009	–	–
95+ years	–	–	0.176	0.097	–	–

*Number: Number of deaths in the population.
**HBMID: Number of deaths from asthma caused by High Body Mass Index
***OAD: Number of asthma-related deaths caused by Occupational Asthmagens
****SMD: Number of asthma-related deaths caused by smoking

Total number of deaths because of asthma (Z=5.515; p<0.001), total percent of death (Z=6.653; p<0.001) and total rate of death variables (total rate of death) by gender. The difference between mean rank (Z=3.977; p<0.001) was statistically significant. It was determined that the number of women who died because of asthma was higher than that of men. The difference between the mean rank of incidence (Z=5.248; p<0.001) and prevalence (Z=6.653; p<0.001) according to gender was also statistically significant (**Table 3**).

Table 3. Death, Incidence, Prevalence: By Gender (years, all ages)

	Both	Female	Male	Female vs Male
Death Number**	82649	46194	36455	Z=5.515; p<0.001
Death Percent***	0.0072	0.0092	0.0057	Z=6.653; p<0.001
Death Rate****	3.90	4.39	3.43	Z=3.977; p<0.001
Incidence*	0.115	0.127	0.102	Z=5.248; p<0.001
Prevelance*	4.981	5.909	4.041	Z=6.653; p<0.001

* Incidence and prevalence; for all age groups, the 30-year percent average is *100.
**Number: Number of deaths in the population
***Percent: Proportion of deaths from a specific cause compared to deaths from all causes
****Rate: Deaths per 100,000 population

Relationships between risk factors that cause asthma-related deaths were examined, and the results are given in Table 4. In all genders (both), HBMID was found to have an inverse, moderately strong correlation with both OAD (Rho=-0.426; p=0.019) and SMD (Rho=-0.417; p=0.022). In women, an inverse and strong correlation was found between HBMID and OAD (Rho=-0.610; p<0.001). No significant relationship was found between HBMID and SMD when both men and women were evaluated separately. Between OAD and SMD, a strong correlation was found in the same direction as women (Rho=0.759; p<0.001); A very strong correlation was found in the same direction in men (Rho=0.985; p<0.001) and all genders (Rho=0.988; p<0.001) (**Table 4**).

Table 4. Relationships between the number of deaths caused by risk factors by gender (years, all ages)

Gender	HBMID** - OAD*		OAD-SMD***		HBMID-SMD	
	Rho	p	Rho	p	Rho	p
Both	-0.426	0.019	0.988	<0.001	-0.417	0.022
Female	-0.610	<0.001	0.759	<0.001	-0.125	0.510
Male	0.299	0.108	0.985	<0.001	0.337	0.069

*OAD: Number of deaths from asthma caused by Occupational Asthmagens
**HBMID: Number of deaths from asthma caused by High Body Mass Index ***SMD: Number of asthma-related deaths caused by smoking

DALYs were compared by gender and are presented in Table 5. It was found that HBMIDALYs for women were almost twice as high as for men (Z=6.653; p<0.001). However, it was determined that OADALYs and SMDALYs for men, on the contrary, were at a level of twice that of women. The DALYs resulting from the three risk factors examined by gender differ (p<0.001) (**Table 5**).

Table 5. Median DALYs score by gender (years, all ages)

DALYs	Both	Female	Male	Female vs Male
HBMIDALYs*	46390.19 (2835.90)	30036.47 (2297.25)	16532.15 (854.02)	Z=6.653; p<0.001
OADALYs**	12873.74 (3879.23)	4603.58 (1179.05)	8251.33 (2785.65)	Z=6.653; p<0.001
SMDALYs***	25429.25 (4289.64)	8277.58 (197.31)	16968.56 (3982.04)	Z=6.653; p<0.001

*HBMIDALYs: DALYs from asthma caused by High Body Mass Index
**OADALYs: Asthma-induced DALYs caused by Occupational Asthmagens
***SMDALYs: DALYs from asthma caused by Smoking

DISCUSSION

Although the incidence, prevalence, and severity of asthma increase with adolescence, they are higher in women.[13] It is estimated that women-specific conditions such as early puberty, pregnancy, and menopause affect asthma.[14] In this study, consistent with the literature, it was found that the number of asthma-related deaths and the incidence and prevalence of asthma were higher in women. It seems that asthma and obesity tend to increase in parallel, and there may be a potential link between these two conditions.[7] As a result of the research, it was determined that HBMID and HBMIDALYs were higher.

In a study, it was determined that 60% of 8239 work-related asthma cases developed by workers in various business lines were women.[15] Exposure of women to various chemicals, especially in jobs such as food, textiles, and cleaning, is associated with higher asthma.[15,16] However, occupational asthma is also said to be unrelated to gender.[17] Men are more likely to be exposed to pyrolysis products, plant-based materials, isocyanates, metals, and metalloids.[18] It is thought that the stimuli causing occupational asthma are also different due to the fact that men and women work in different work environments. In this study, unlike the literature, occupational asthma was found to lead to higher mortality and DALYs in men. This can be explained by the fact that men are exposed to more work-related stimuli, as the labor force participation rate for men aged 15 and over is 70.3% in Turkey.[19] The fact that smoking rates are higher in men indicates it may be a more effective risk factor than women.[20] In this study, causes of death because of asthma caused by smoking and the DALYs score were found to be higher in males.

CONCLUSION

Asthma is a disease that affects both children and adults and has high DALYs because of the disability it causes. Although the risk factors that cause asthma cannot be completely eliminated, policies aimed at least reducing them will prevent people from falling behind in social and work life, as well as improving their health status. The incidence, prevalence, and deaths of the disease are higher in women. However, when evaluated according to risk factors, smoking, which is one of the occupational and behavioral factors in men HBMI, which is one of the metabolic factors, are seen to cause higher deaths and DALYs in women. For this reason, it is thought that following different policies according to gender will be effective in preventing the disease and reducing the damage caused by the disease. According to the study findings, for men, reducing exposure to factors that cause asthma risk in the work environment and promoting smoking cessation; For women, it can be said that the prevention of obesity will be beneficial.

ETHICAL DECLARATIONS

Ethics Committee Approval: Since public data was used in this study, there is no need for an ethics committee decision.

Informed Consent: Since public data was used in this study, there is no need for an informed consent.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Zhang X, Köhl J. A complex role for complement in allergic asthma. *Expert Rev Clin Immunol.* 2010;6(2):269-77. doi:10.1586/eci.09.84
2. WHO. Asthma. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/asthma. Accessed 16.04.2023
3. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 2020;396(10258):1204-1222. doi:10.1016/s0140-6736(20)30925-9
4. Birdi K, Beach J. Management of sensitizer-induced occupational asthma: avoidance or reduction of exposure? *Curr Opin Allergy Clin Immunol.* 2013;13(2):132-7. doi:10.1097/ACI.0b013e32835ea249
5. Clark VL, Gibson PG, Genn G, Hiles SA, Pavord ID, McDonald VM. Multidimensional assessment of severe asthma: A systematic review and meta-analysis. *Respirology.* 2017;22(7):1262-1275. doi:10.1111/resp.13134
6. Louisias M, Ramadan A, Naja AS, Phipatanakul W. The effects of the environment on asthma disease activity. *Immunol Allergy Clin North Am.* 2019;39(2):163-175. doi:10.1016/j.iac.2018.12.005
7. Noal RB, Menezes AM, Macedo SE, Dumith SC. Childhood body mass index and risk of asthma in adolescence: a systematic review. *Obes Rev.* 2011;12(2):93-104. doi:10.1111/j.1467-789X.2010.00741.x
8. Tinuoye O, Pell JP, Mackay DF. Meta-analysis of the association between secondhand smoke exposure and physician-diagnosed childhood asthma. *Nicotine Tob Res.* 2013;15(9):1475-83. doi:10.1093/ntr/ntt033
9. WHO (2022) Global health estimates: Leading causes of DALYs, https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/global-health-estimates-leading-causes-of-dalys. Accessed 16.04.2023.
10. Arnesen T, Nord E. The value of DALY life: problems with ethics and validity of disability adjusted life years. *BMJ.* 1999;319(7222):1423-5. doi:10.1136/bmj.319.7222.1423
11. GBD. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Accessed 01.04.2023, https://vizhub.healthdata.org/gbd-results/. Accessed 01.04.2023
12. The Institute for Health Metrics and Evaluation (IHME). Country profiles. Available Online: https://www.healthdata.org/results/country-profiles. Accessed 19.04.2023.
13. Zein JG, Erzurum SC. Asthma is Different in Women. *Curr Allergy Asthma Rep.* 2015;15(6):28. doi:10.1007/s11882-015-0528-y
14. Fuseini H, Newcomb DC. Mechanisms Driving Gender Differences in Asthma. *Curr Allergy Asthma Rep.* 2017;17(3):19. doi:10.1007/s11882-017-0686-1
15. White GE, Seaman C, Filios MS, et al. Gender differences in work-related asthma: surveillance data from California, Massachusetts, Michigan, and New Jersey, 1993-2008. *J Asthma.* 2014;51(7):691-702. doi:10.3109/02770903.2014.903968
16. Ahmed AS, Ibrahim DA, Hassan TH, Abd-El-Azem WG. Prevalence and predictors of occupational asthma among workers in detergent and cleaning products industry and its impact on quality of life in El Asher Men Ramadan, Egypt. *Environ Sci Pollut Res.* 2022;29(23):33901-33908. doi:10.1007/s11356-022-18558-8
17. Caldeira RD, Bettiol H, Barbieri MA, Terra-Filho J, Garcia CA, Vianna EO. Prevalence and risk factors for work related asthma in young adults. *Occup Environ Med.* 2006;63(10):694-9. doi:10.1136/oem.2005.025916
18. Boulet L-P, Lavoie KL, Raherison-Semjen C, Kaplan A, Singh D, Jenkins CR. Addressing sex and gender to improve asthma management. *NPJ Primary Care Respir Med.* 2022;32(1):56. doi:10.1038/s41533-022-00306-7
19. TÜİK. İstatistiklerle Kadın, 2022. https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Kadin-2022-49668. Accessed 16.04.2023
20. Ricciardolo FLM, Levra S, Sprio AE, et al. Asthma in the real-world: the relevance of gender. *Int Arch Allergy Immunol.* 2020;181(6):462-466. doi:10.1159/000506808

Journal of
Pulmonology and
Intensive Care

Original Article

DOI: 10.51271/JOPIC-0007

Evaluation of human neutrophil gelatinase-associated lipocalin level in asthma-COPD overlap syndrome of elderly patients

Serap Duru[1], Fatma Uçar[2]

[1]Department of Chest Disease, Ankara Etlik City Hospital, Ankara, Turkey
[2]Department of Biochemistry, Dışkapı Yıldırım Beyazıt Health Practice and Research Centers, University of Health Science, Ankara, Turkey

Cite this article: Duru S, Uçar F. Evaluation of human neutrophil gelatinase-associated lipocalin level in asthma-COPD overlap syndrome of elderly patients. *J Pulmonol Intens Care*. 2023;1(2):32-37.

Corresponding Author: Serap Duru, akcalis@hotmail.com

Received: 10/04/2023 ◆ **Accepted**: 04/05/2023 ◆ **Published**: 22/05/2023

ABSTRACT

Aims: Human neutrophil gelatinase-associated lipocalin (NGAL) is a protein considered as a noninvasive prognostic biomarker in Asthma-COPD overlap syndrome (ACO). In this study we aimed to show the usability of NGAL as a biomarker in ACO characterized with airway inflammation in over 65 years old.

Methods: Three patient groups (Group I: COPD, n: 50, Group II: Asthma, n:50, Group III: ACO, n:50) and a healhty non smoker group (Group IV, n:50) are taken into study. The serum NGAL levels of groups are compared. In Group I, II, III the level of serum NGAL is compared with the age, duration of smoking (pocket/year), number of attack per year, respiratory function values, serum C reaktive protein (CRP, mg/dL), serum IgE (IU/mL) and blood neutrophil-to-lymphocyte rate and atopy.

Results: In patients having ACO when the maximum level of serum exist, it is observed that serum NGAL level is increased as the number of attacks is increased ($p<0.002$). On the other hand in the patients having ACO there was also positive correlation between NLR and serum NGAL level ($p<0.05$).

Conclusion: The increase in serum NGAL levels in chronic inflammatory lung diseases suggests that serum NGAL levels can be used as a biomarker to assess inflammation severity

Keywords: Elderly, human neutrophil gelatinase-associated lipocalin, asthma-COPD overlap syndrome

INTRODUCTION

Asthma is a heteregenous chronic airway diseases which leads to reversible airflow obstruction based on innate and adaptive immune responses. Heterogenity of asthma is due to genetic and environmental reasons, chronic aiway diseases affecting 1-18% of the population.[1] In the majority of patients are underlying atopy. Inflammatory cell-derived mediators cause increased vascular permeability, mucosal edema, bronchial smooth muscle hypertrophy and subepithelial fibrosis.[2-6] Chronic obstructive pulmonary disease (COPD); It is a disease characterized by progressive airflow restriction that is not fully reversible. This disease develops as a result of an inflammatory process against harmful gases and particles, especially cigarette smoke. Inflammation is not only limited to the lungs, but also shows systemic features.[7] COPD, which is a preventable and treatable disease, progresses with exacerbations that increase in severity and frequency. Chronic airway obstruction in COPD develops due to narrowing of small airways and parenchymal destruction. Chronic inflammation causes structural changes in the small airways. This inflammatory process and parenchymal destruction lead to loss of alveoli and a decrease in the elastic return pressure of the lungs.[8] Asthma-COPD overlap (ACO) refers to a group of poorly studied and characterised patients reporting with disease presentations of both asthma and COPD, thereby making both diagnosis and treatment challenging for the clinicians.[9-11] ACO is defined in the GINA and GOLD guidelines as "the accompanying of asthma and COPD characteristics in patients with persistent airflow restriction at close rates". ACO can be defined as symptoms accompanying increased airway sensitivity, reversible airway obstruction and persistent airflow restriction. While at present there is no general consensus on definition or defining features for this subgroup of patients, there is broad agreement that they experience frequent exacerbations.[12-14]

The prevalence of ACO is 15-55% in the population ACO has been found to be a disease of advanced age in recent studies. They exhibit a higher burden in terms of both mortality and morbidity in comparison to patients with only asthma or COPD. The pathophysiology of the disease and its existence as a unique disease entity remains unclear.[15,16]

Neutrophil Gelatinase-associated Lipocalin (NGAL), also known as neutrophil glucosaminidase-associated lipocalin, is a 178 amino acid, 25 kDa protein synthesized in neutrophils and epithelial cells. Gene expression has been demonstrated in the

uterus, prostate, salivary glands, lung, trachea, stomach, colon and kidney. Neutrophil gelatinase-related lipocalin production increases in humans in response to ACO and can be detected in serum at a very early stage.[17-20]

In recent years, in studies conducted in ACO patients, there are limited numbers of publications about the high serum lipocalin levels associated with human neutrophil gelatinosis and that it is associated with the severity of the disease. This study was planned considering that there is a limited amount of literature information in association with NGAL and asthma, COPD and ACO in elderly patients.

METHODS

Ethics

The study was carried out with the permission of University of Health Science Dışkapı Yıldırım Beyazıt Health Pratctice and Research Centers Ethics Committee (Date: 23.03.2015, Decision No: 21.14). The study was planned in accordance with the suggestions of the Helsinki Document and our hospital ethic commission (23.03.2015/21.14). Signed consent forms were obtained from all the patients who volunteered. This study was not supported by any organization. There isn't conflicts of interest, financial or otherwise in this study.

Patients

Two hundred and sixty patients aged 65 years and older (T hey were diagnosed with ACO, COPD and asthma according to the GOLD, GINA 2020 criteria between May 2015 and December 2020, which was done our hospital. However, the full article has not previously been published. Three patient groups (Group I: COPD, n: 70, Group II: Asthma, n: 70), Group III: ACO, n:70) and a healhty non smoker group (Group IV, n:50) are taken into study. Asthma, ACO and COPD was excluded in the control group by demographic data, physical examination and respiratory function tests. Detailed physicals exams, detailed blood tests, height, weight and neck circumference measurements were conducted. The body mass index (BMI, kg/m²) of each patient was calculated by dividing the body weight in kilograms by the square of the patient's height in meters. Assuming its benefit in exclusion of the respiratory system pathologies, posteroanterior chest radiography was performed. Pulmonary function tests were performed in the respiratory laboratory of our hospital, using a Jaeger brand spirometer according to the criteria of American Thoracic Society (ATS). Forced expiratory volume in one second (FEV1, liters), and forced vital capacity (FVC, liters), and FEV1 to FVC (%) values are measured at least 3 times, and optimal values were recorded. Twentyfour of well controlled asthmatic patients were categorized as mild persistant, 46 of them as moderate persistant asthma according to GINA before treatment. The patients also underwent physical examinations. One or more positive results to allergens in skin prick test (Allergopharma, Germany) was accepted as atopy. According to previous skin prick test results of patients regullary followed in our clinics, 15 asthma patients (3 mild peristant, 9 moderate persistant) and three ACO patients had atopy.

The severity of the COPD was categorized into moderate (n: 31, FEV1/FVC<0.70,50%≤FEV1<80% predicted), and severe (n:39, FEV1/FVC<0.70, 30%≤FEV1<50% predicted) according to GOLD criteria. Patient with ACO was categorized according to GINA and GOLD criteria.[20] The treatment of our patient's protocols was explained to GOLD and GINA criteria. Anemia was defined as Hb<12 g/dl in male. Baseline arterial oxygen saturation was defined ≤88%. Our exclusion criteria were an acute COPD, ACO and exacerbations in the last 3 months (increased cough, dyspnea, sputum production, and/or purulence), other acute and chronic diseases, a blood transfusion in the last 6 months, anti-inflammatory therapy (oral, parenteral systemic glucocorticosteroids) within the last 3 months, and anemia within the last 6 months, malignancy and pregnancy.

Laboratory

In all patient groups and control group included in the study, blood and serum samples for full blood testing were taken in the morning on an empty stomach. Serum CRP (0-6 mg/L), serum Ig E (0-180 IU/mL), serum neutrophil (%), lymphocyte (%) levels were assessed using standard laboratory methods. The blood sample drawn for the measurement of NGAL were collected early in the morning after a minimum of 10 hours fasting and centrifuged for 10 min at 3000 rpm, and serum was stored at -80°C in aliquots until the day of analysis. Serum NGAL levels were measured using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA), according to the instructions of the producer company (Hangzhou Eastbiopharm Co. Ltd., Hangzhou, China). Results were given as ng/mL. The intra-assay coefficient of variation (CV) was <10% and the inter-assay CV was 12%. Chest radiographs were evaluated to exclude other pathologies. The NLR was obtained by dividing the absolute number of neutrophils by the absolute number of lymphocytes. The data were expressed as a percentage value (i.e.: 2.25%).

Statistical Analysis

Statistical analyses were performed using (Predictive Analytics SoftWare) version 20. Descriptive results for numerical variables were expressed as mean ± standard deviation; categorical variables were expressed as frequency and percentage. Chi-square analysis or Fisher's exact test, where appropriate, was used to compare proportions in different groups. There was said to be a statistically significant difference between groups when P<0.005. In that case, difference groups were determined by the Mann-Whitney U test and Bonferroni correction.The relationship of serum NGAL levels with other variables was examined using the Spearman Correlation coefficient.

RESULTS

Demographic and laboratory data for the 260 patients and control group monitored at our clinic were demonstrated in **Table 1**. The mean serum NGAL level of the control group was found to be 211.210 (102.85-800.49) ng/ml. Serum NGAL level of asthmatic patients was 176.280 (82.78-976.59) ng/ml while the mean serum NGAL level of the patients with COPD was found to be 221.901 (97.84-1938.62) ng/ml and with ACO was found to be 269.146 (153.70-1796.78). There was a significant difference between serum NGAL levels of ACO patients (p=0.002). Except ACO group, all of the patient groups and control group included in the study had C-reactive protein (CRP) levels within the normal limits (upper normal level, 6 mg/L). **Figure 1** shows the box plot graphs of serum NGAL level in all patients groups. **Figure 2** shows tho box plot FEV1(L) level of patients and control group. **Figure 3** shows the box plot FEV1/FVC (L) level of patients and control group. Forced expiratory volume in one second (FEV1) and FEV1/FVC ratio was higher patients with asthma and control groups. **Figure 4**

shows the box plot acute exacerbation of patients with Asthma, COPD, ACO. Acute exacerbation was also high in patients with ACO. Relationships between the serum NGAL levels and other variables were demonstrated in **Table 2**. The serum NGAL levels was found significantly higher in patients with ACO patients compared to other groups. It was found that this height was positively correlated with number of attack per year ($p<0.05$). On the other hand in the patients having ACO there was also positive correlation between NLR and serum CRP level and serum NGAL ($p<0.05$). There was no other relation found among the other variables. **Figure 5** shows the box plot graphs of the relationship between smoking and serum NGAL level in patients with ACO.Serum NGAL was increasing in proportion to smoking.But not statistically significant ($p>0.05$).

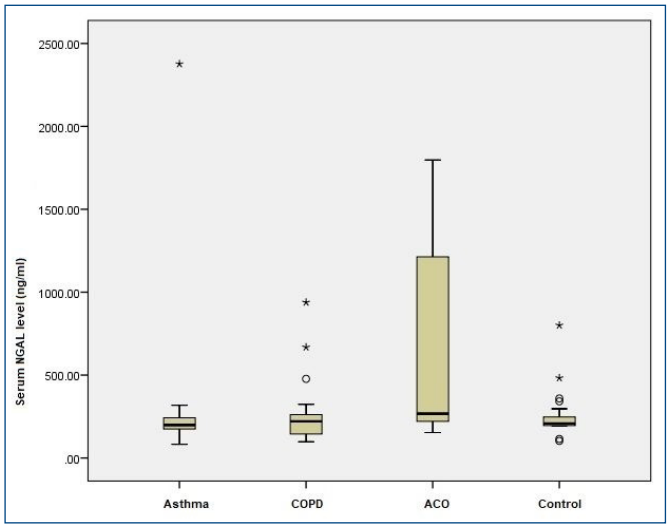


Figure 1. The box plot graphs of serum NGAL level in all patients groups

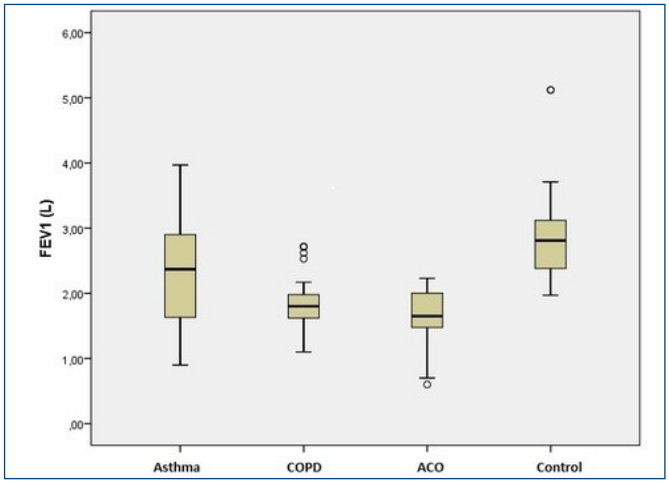


Figure 2. FEV1(L) level of patients and control group.

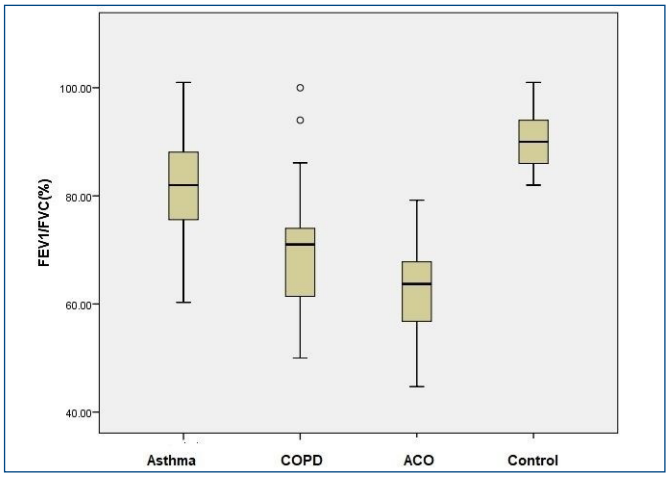


Figure 3. The box plot FEV1/FVC (L) level of patients and control group.

Table 1. Demographic information and laboratory characteristics of patient groups and control group.

Variables	Asthma (n:70)	COPD (n:70)	ACO (n:70)	Control (n:50)
Age (year)	65.10 ± 10.98	69.80 ± 11.30	74.06 ± 11.57	65.06 ± 15.57
Sex (Female/Male)	47/23	28/42	31/39	33/17
Smoking (pack-year)	-	32.91 ± 23.11	25.50 ± 8.51	-
Dieasase year	12.40 ± 3.39	13.76 ± 5.06	11.03 ± 5.62	-
Exacerbation (/year)	1 (0–2)	2 (1–4)	3 (2–4)	-
BMI (kg/m²)	27.34 ± 3.70	26.49 ± 4.64	26.19 ± 4.09	28.29 ± 5.09
FEV1/FVC (%)	72.45 ± 7.65	60.34 ± 12.08	48.17 ± 11.67	92.45 ± 7.75
FEV1(%)	73.36 ± 6.48	65.20 ± 6.30	50.12 ± 6.13	90.36 ± 5.47
Total IgE level (1–83 IU/ml)	137.60 (47-1211)	48.9 (10–81)	151 (125–1825)	21 (9–67)
Atopy (+)	15			
C-reactive protein (CRP, 0–6 mg/L)	5.4 ± 3.5	7.9.±4.1	10.7 ± 5.7	3.9 ± 2.8
Neutrophil (×10³/mm³)	4.05 ± 2.53	4.91 ± 1.53	6.25 ± 3.03	4.70 ± 1.71
Lymphocyte (×10³/mm³)	1.08 ± 0.66	1.45 ± 0.73	1.71 ± 0.42	1.91 ± 0.24
Blood neutrophil to lymphocyte ratio	2.92 ± 1.69	3.22 ± 1.06	4.37 ± 6.09	2.72 ± 1.44
Serum HNGAL level (ng/ml)	176.280 (82.78-976.59)	221.901 (97.84-1938.62)	269.146 (153.701–796.78)	207.110 (102.85-800.49)

Table 2. Relationships between the serum NGAL levels and other variables.

Variables	Asthma (n:70)		COPD (n:70)		ACO (n:70)	
	r	p	r	p	r	p
Age (year)	0,315	0,085	0,191	0,369	0,061	0,731
Disease year	0,102	0,591	0,337	0,070	0,158	0,404
Exacerbation (/year)	-,189	,327	,334	,077	0,248**	0,021
BMI (kg/m²)	0,159	0,402	0,067	0,724	0,160	0,400
FEV1/FVC (%)	0,025	0,899	0,193	0,311	0,235	0,237
FEV1(%)	0,031	0,831	0,147	0,387	0,185	0,358
Total IgE level (1–83 IU/ml)	0,168	0,398	0,193	0,307	0,234	0,129
Blood neutrophil to lymphocyte ratio	0,162	0,407	0,033	0,841	0.280**	0,012
C-reactive protein (CRP, 0–6 mg/L)	-0.01	0.9	-0.04	0.7	0.614**	0.011
Atopy (+)	-0.02	0.7	-	-	0.22	0.091

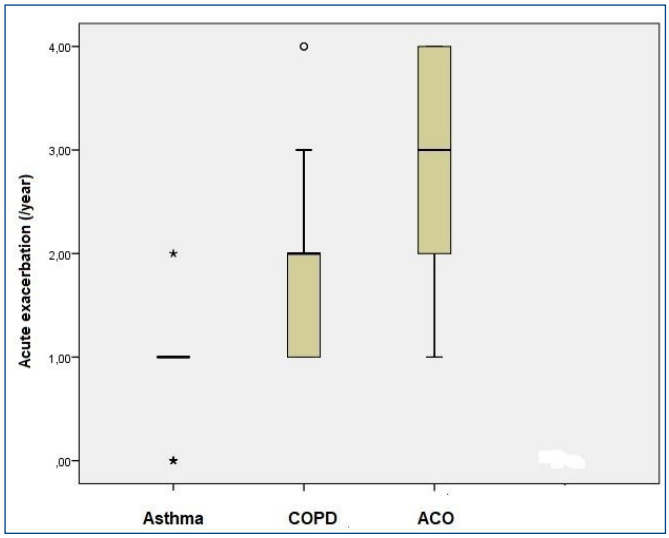


Figure 4. The box plot acute exacerbation of patients with Asthma, COPD, ACO.

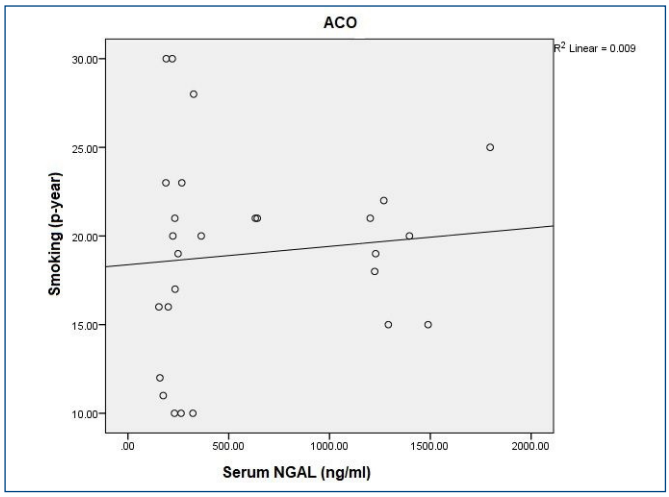


Figure 5. The box plot graphs of the relationship between smoking and serum NGAL level in patients with ACO.

DISCUSSION

The aim of this study is to compare and analyse serum NGAL levels at chronic inflamatuar lung disease such as asthma, COPD, ACO and to evaluate the clinical utility of serum NGAL as a predictive marker for these disease for elderly patients. In this study, we found that serum NGAL level was higher in ACO group than COPD, asthma and control groups. Moreover, serum NGAL level is increased as the number of attacks is increased (p: 0.021) with ACO patients. On the other hand in the patients having ACO, there was also positive correlation between blood NLR and serum CRP levels with serum NGAL levels. There was no correlation found among the other variables. Chronic inflammatory lung diseases such as COPD, asthma and ACO are among the commonly seen reasons of death worldwide. Studies have shown that during stable period and exacerbations in patients with chronic inflammatory lung diseases increase both local and systemic inflammatory response. In recent years, serum NGAL in inflammation, endothelial dysfunction, angiogenesis and remodeling have been reported to increases. Until now, NGAL's research continues as an inflammatory marker in the various diesases. NGAL is expressed at low levels in different tissues, such as kidney, trachea, lungs, stomach, and colon, and its expression increases noticeably in inflammation. Chronic inflammatory lung diseases are one of them.[21-23]

There has been limited number of studies related with NGAL in lung diseases. In first studies, serum NGAL is significantly elevated in the bronchoalveolar lavage fluid (BALF) and induced sputum of COPD patients. In normal human lung tissue, NGAL is constitutively expressed within tracheal goblet cells and in type II pneumocytes. An increase in the level of inflammation occurs with the progression of chronic inflammatory lung diseases. In our study, the detection of increased serum NGAL levels in elderly patients with chronic inflammatory lung diseases in the stable period supported that, rather than being restricted to the lung therefore being local, they are systemic inflammatory diseases.[24-26] In previous studies, it was reported that serum NGAL expression increased in various malignancies and it is a prognostic factor in these cancers and can be used in follow-up, after treatment. After acute ischemic and nephrotoxic injury, serum NGAL expression from the renal epithelium increases in response to inflammation. Serum NGAL exists as an acute phase protein based on high levels in serum, epithelial, urine and fecal levels of patients with active inflammatory disease.[27-30] There is no sufficient data on serum NGAL levels during exacerbation periods in ACO. Our study showed serum NGAL in elderly patients having ACO when the maximum level of serum exist, it is observed that serum NGAL level is increased as the number of attacks is increase. Our findings are supported by the other studies for higher serum levels of NGAL in elderly patients. We found serum NGAL level to be highest in ACO as compared to asthma, COPD and controls. Our results are in good agreement with reports suggesting higher levels of NGAL in ACO as compared to asthma. Further, a significant negative correlation was observed between serum NGAL and lung function in ACO patients. Our findings are supported by the work of Gao, et al, where an increased NGAL expression in sputum has been independently correlated with degree of airflow limitation in ACO.[24]

Studies have shown mice lacking serum NGAL gene are more sensitive to some gram (-) bacteria. In addition, mortality rates were found to be higher in sepsis compared to normal mice. Therefore, serum NGAL is defined as an essential component of innate immunity against bacterial infections. NGAL production increases in bacterial infections and NGAL levels in tissues are used to differentiate bacterial-viral infections. Activated neutrophils secretes matrix metalloprotease 9 (MMP-9). NGAL binds to MMP-9 and prevents prolonged collagen degradation. These actions of NGAL are of particular interest in relation to patients with chronic inflammatory lung diseases especially development of emphysema and airway wall remodeling.[31-33] In a study on NGAL, sputum levels of NGAL were significantly higher in patients with ACO compared with subjects without ACO and that level of NGAL was related to important ACO characteristics.[34] NGAL is actively secreted from both neutrophils and epithelial cells. The upregulation of NGAL transcription in neutrophils and epithelial cells involves fundamental upstream inflammatory pathways, such as activation of nuclear factor- k B, interleukin-1 activation, and interaction between microbial products and certain toll-like receptors. NGAL may be a marker of several upstream inflammatory pathways, reflecting several processes potentially involved in the pathogenesis of COPD and ACO . In our study, we

found that both NLR and exacerbation rate were positively correlated with increasing serum NGAL level, which supports the relationship between increased neutrophil rate and NGAL in inflammation especially patients in ACO.

Systemic inflammation in ACO is similar to COPD. Serum NGAL value was found close to each other in ACO and COPD groups in our study. This result may support the similarity of inflammatory events between COPD and ACO. In another study, the sputum levels of NGAL were significantly increased in ACO when compared with COPD and asthma groups. The sputum NGAL levels might be related to airway inflammation and low-grade microbial colonization, which predispose patients with ACO to acute viral infections and exacerbations.

The present study aimed to investigate the potential of NLR, as a prognostic markers in patients with chronic inflammatory lung diseses. It has been demonstrated that NLR may be a useful predictor of systemic inflammation and with prognosis of many cardiovascular diseases, malignancies and chronic inflammatory diseases.[35-37] Taking this idea into account, some studies focused on NLR which are considered among the markers of systemic inflammatory response for COPD, ACO and asthma. One of these have shown that increase in the ratio of circulating blood NLR levels may serve as a marker of systemic inflammation for ACO, COPD patients. The patients with stable disease and healthy controls have shown lower NLR values than the patients with COPD exacerbation, according to the study done by Lee, et al.[38] In another study by Lee et al, they found NLR values increased with restriction of airflow limitation. They tought that the change in NLR was due to COPD itselfs.[39] So far, the studies reviewed showed that can be used to predict COPD prognosis and mortality. In another study, neutrophils and NLR, as indicators of circulating immune complexes, were found higher in patients with COPD and ACO than those in the healthy population. They thougt that NLR may be used as a biomarker to distinguish and diagnose COPD and ACO.[40] With a different perspetcive, Li et al.[41] they found the level of NLR similar in COPD and ACO patients. In another study found that the NLR ratio increased in parallel with the severity of COPD.[42] Similar results were found in our study. The NLR ratio increased with the aggravation of inflammation. Our patient with ACO groups had high serum CRP levels. Ultimately ACO and COPD are associated with systemic inflammation. The increase NLR and CRP may supports this situation.[43-47] Due to the high number of exacerbation period for ACO, we think that the role of inflammatory mechanisms may increase in this desase.

CONCLUSION

As a result; especially in elderly patients, there is no known prognostic biomarker for ACO. In patients with chronic inflammatory lung diseases, NGAL may be a systemic useful biomarker reflecting the inflammation level. In additional to chronic systemic inflammation may explain an parellel increase in NLR value, CRP and serum NGAL. This study has some limitations. Additional studies are needed for clinical evaluation of the progression of chronic inflammatory lung diseases. As our study was conducted with a small sample group, the study should be supported with larger scale studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Science Dışkapı Yıldırım Beyazıt Health Practice and Research Centers Ethics Committee (Date: 23.03.2015, Decision No: 21.14).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Global Initiative for Asthma. 2022 GINA Main Report: Global strategy for asthma management and prevention. Available online: www.ginasthma.org (updated 2020).
2. Barnes PJ. Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol.* 2008;8(3):183-192. doi:10.1038/nri2254
3. Brusselle GG, Maes T, Bracke KR. Eosinophils in the spotlight: Eosinophilic airway inflammation in nonallergic asthma. *Nat Med.* 2013;19(8):977-979. doi:10.1038/nm.3300
4. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. *J Allergy Clin Immunol.* 2011;128(3):451-464. doi:10.1016/j.jaci.2011.04.047
5. Borger P, Tamm M, Black JL, Roth M. Asthma: is it due to an abnormal airway smooth muscle cell?. *Am J Respir Crit Care Med.* 2006;174(4):367-372. doi:10.1164/rccm.200501-082PP
6. Barnes PJ. Pathophysiology of asthma. *Br J Clin Pharmacol.* 1996;42(1):3-10. doi:10.1046/j.1365-2125.1996.03721.x
7. Global Initiative for Chronic Obstructive Lung Disease (GOLD).2020 GlobalStrategy for Prevention, Diagnosis and Management of COPD. Available from:http://goldcopd.org.
8. Higham A, Quinn AM, Cançado JED, Singh D. The pathology of small airways disease in COPD: historical aspects and future directions. *Respir Res.* 2019;20(1):49. doi:10.1186/s12931-019-1017-y
9. Sin DD, Miravitlles M, Mannino DM, et al. What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion. *Eur Respir J.* 2016;48(3):664-673. doi:10.1183/13993003.00436-2016
10. Gibson PG, Simpson JL. The overlap syndrome of asthma and COPD: what are its features and how important is it?. *Thorax.* 2009;64(8):728-735. doi:10.1136/thx.2008.108027
11. Diagnosis of Disease of Chronic Airflow Limitation: Asthma COPD and Asthma-COPD Overlap Syndrome (ACOS) 2014. Available from:http://www.ginasthma.org/orhttp://goldcopd.org
12. Rothe T, Spagnolo P, Bridevaux PO, et al. Diagnosis and management of asthma - the Swiss guidelines. *Respiration.* 2018;95(5):364-380. doi:10.1159/000486797
13. Kauppi P, Kupiainen H, Lindqvist A, et al. Overlap syndrome of asthma and COPD predicts low quality of life. *J Asthma.* 2011;48(3):279-285. doi:10.3109/02770903.2011.555576
14. Miravitlles M, Soriano JB, Ancochea J, et al. Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir Med.* 2013;107(7):1053-1060. doi:10.1016/j.rmed.2013.03.007
15. Weatherall M, Travers J, Shirtcliffe PM, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. *Eur Respir J.* 2009;34(4):812-818. doi:10.1183/09031936.00174408
16. Hardin M, Silverman EK, Barr RG, et al. The clinical features of the overlap between COPD and asthma. *Respir Res.* 2011;12(1):127. doi:10.1186/1465-9921-12-127
17. Kjeldsen L, Bainton DF, Sengeløv H, Borregaard N. Identification of neutrophil gelatinase-associated lipocalin as a novel matrix protein of specific granules in human neutrophils. *Blood.* 1994;83(3):799-807.
18. Chakraborty S, Kaur S, Guha S, Batra SK. The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. *Biochim Biophys Acta.* 2012;1826(1):129-169. doi:10.1016/j.bbcan.2012.03.008
19. Sivalingam Z, Larsen SB, Grove EL, Hvas AM, Kristensen SD, Magnusson NE. Neutrophil gelatinase-associated lipocalin as a risk marker in cardiovascular disease. *Clin Chem Lab Med.* 2017;56(1):5-18. doi:10.1515/cclm-2017-0120

20. Global Initiative for Asthma, Global Initiative for Chronic Obstructive Lung Disease, Diagnosis of Disease of Chronic Airflow Limitation. Asthma, COPD, and asthma–COPD overlap syndrome (ACOS); 2015. Available from: http://www.ginasthma.org/. Accessed November4, 2020.
21. Ghosh N, Choudhury P, Kaushik SR, et al. Metabolomic fingerprinting and systemic inflammatory profiling of asthma COPD overlap (ACO). *Respir Res.* 2020;21(1):126. doi:10.1186/s12931-020-01390-4
22. Cowland JB, Sørensen OE, Sehested M, Borregaard N. Neutrophil gelatinase-associated lipocalin is up-regulated in human epithelial cells by IL-1 beta, but not by TNF-alpha. *J Immunol.* 2003;171(12):6630-6639. doi:10.4049/jimmunol.171.12.6630
23. Wang Y, Jia M, Yan X, et al. Increased neutrophil gelatinase-associated lipocalin (NGAL) promotes airway remodelling in chronic obstructive pulmonary disease. *Clin Sci (Lond).* 2017;131(11):1147-1159. doi:10.1042/CS20170096
24. Gao J, Iwamoto H, Koskela J, et al. Characterization of sputum biomarkers for asthma-COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis.* 2016;11:2457-2465. doi:10.2147/COPD.S113484
25. Keatings VM, Barnes PJ. Granulocyte activation markers in induced sputum: comparison between chronic obstructive pulmonary disease, asthma, and normal subjects. *Am J Respir Crit Care Med.* 1997;155(2):449-453. doi:10.1164/ajrccm.155.2.9032177
26. Bchir S, Nasr HB, Bouchet S, et al. Concomitant elevations of MMP-9, NGAL, proMMP-9/NGAL and neutrophil elastase in serum of smokers with chronic obstructive pulmonary disease. *J Cell Mol Med.* 2017;21(7):1280-1291. doi:10.1111/jcmm.13057
27. Treeprasertsuk S, Wongkarnjana A, Jaruvongvanich V, et al. Urine neutrophil gelatinase-associated lipocalin: a diagnostic and prognostic marker for acute kidney injury (AKI) in hospitalized cirrhotic patients with AKI-prone conditions. *BMC Gastroenterol.* 2015;15:140. doi:10.1186/s12876-015-0372-5
28. Lorenzo-Gómez MF, Flores-Fraile MC, Márquez-Sánchez M, et al. Increased urinary markers of kidney damage in the institutionalized frail elderly due to recurrent urinary tract infections. *Ther Adv Urol.* 2020;12:1756287220974133. doi:10.1177/1756287220974133
29. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet.* 2005;365(9466):1231-1238. doi:10.1016/S0140-6736(05)74811-X
30. Cao J, Lu X, Gao F, Zhang X, Xia X, Sun H. Assessment of neutrophil gelatinase-associated lipocalin as an early biomarker for canine renal ischemia-reperfusion injury. *Ann Transl Med.* 2020;8(22):1491. doi:10.21037/atm-20-6314
31. Navratilova Z, Kolek V, Petrek M. Matrix metalloproteinases and their inhibitors in chronic obstructive pulmonary disease. *Arch Immunol Ther Exp (Warsz).* 2016;64(3):177-193. doi:10.1007/s00005-015-0375-5
32. Navratilova Z, Kolek V, Petrek M. Matrix metalloproteinases and their inhibitors in chronic obstructive pulmonary disease. *Arch Immunol Ther Exp (Warsz).* 2016;64(3):177-193. doi:10.1007/s00005-015-0375-5
33. Williams KA, Labidi-Galy SI, Terry KL, et al. Prognostic significance and predictors of the neutrophil-to-lymphocyte ratio in ovarian cancer. *Gynecol Oncol.* 2014;132(3):542-550. doi:10.1016/j.ygyno.2014.01.026
34. Kacan T, Babacan NA, Seker M, et al. Could the neutrophil to lymphocyte ratio be a poor prognostic factor for non small cell lung cancers?. *Asian Pac J Cancer Prev.* 2014;15(5):2089-2094. doi:10.7314/apjcp.2014.15.5.2089
35. Paliogiannis P, Scognamillo F, Bellomo M, et al. Neutrophil to lymphocyte ratio as a predictor of thyroid papillary carcinoma. *Act Med Mediterr.* 2015; 31: 371-5.
36. Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. *Br J Cancer.* 2013;109(2):416-421. doi:10.1038/bjc.2013.332
37. Lee SJ, Lee HR, Lee TW, et al. Usefulness of neutrophil to lymphocyte ratio in patients with chronic obstructive pulmonary disease: a prospective observational study. *Korean J Intern Med.* 2016;31(5):891-898. doi:10.3904/kjim.2015.084
38. Lee H, Um SJ, Kim YS, et al. Association of the neutrophil-to-lymphocyte ratio with lung function and exacerbations in patients with chronic obstructive pulmonary disease. *PLoS One.* 2016;11(6):e0156511. doi:10.1371/journal.pone.0156511
39. Paliogiannis P, Fois AG, Sotgia S, et al. Neutrophil to lymphocyte ratio and clinical outcomes in COPD: recent evidence and future perspectives. *Eur Respir Rev.* 2018;27(147):170113. doi:10.1183/16000617.0113-2017
40. Pilaczyńska-Cemel M, Gołda R, Dąbrowska A, Przybylski G. Analysis of the level of selected parameters of inflammation, circulating immune complexes, and related indicators (neutrophil/lymphocyte, platelet/lymphocyte, CRP/CIC) in patients with obstructive diseases. *Cent Eur J Immunol.* 2019;44(3):292-298. doi:10.5114/ceji.2019.87498
41. Li M, Yang T, He R, et al. The value of inflammatory biomarkers in differentiating asthma-COPD overlap from COPD. *Int J Chron Obstruct Pulmon Dis.* 2020;15:3025-3037. doi:10.2147/COPD.S273422
42. Sakurai K, Chubachi S, Irie H, et al. Clinical utility of blood neutrophil-lymphocyte ratio in Japanese COPD patients. *BMC Pulm Med.* 2018;18(1):65. doi:10.1186/s12890-018-0639-z
43. Lenártová P, Kopčeková J, Gažarová M, Mrázová J, Wyka J. Biochemical parameters as monitoring markers of the inflammatory reaction by patients with chronic obstructive pulmonary disease (COPD). *Rocz Panstw Zakl Hig.* 2017;68(2):185-190.
44. Pilaczyńska-Cemel M, Gołda R, Dąbrowska A, Przybylski G. Analysis of the level of selected parameters of inflammation, circulating immune complexes, and related indicators (neutrophil/lymphocyte, platelet/lymphocyte, CRP/CIC) in patients with obstructive diseases. *Cent Eur J Immunol.* 2019;44(3):292-298. doi:10.5114/ceji.2019.87498
45. Fu JJ, McDonald VM, Gibson PG, Simpson JL. Systemic inflammation in older adults with asthma-COPD overlap syndrome. *Allergy Asthma Immunol Res.* 2014;6(4):316-324. doi:10.4168/aair.2014.6.4.316
46. Menezes AMB, Montes de Oca M, Pérez-Padilla R, et al. Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma. *Chest.* 2014;145(2):297-304. doi:10.1378/chest.13-0622
47. Zeki AA, Schivo M, Chan A, Albertson TE, Louie S. The asthma-COPD overlap syndrome: a common clinical problem in the elderly. *J Allergy (Cairo).* 2011;2011:861926. doi:10.1155/2011/861926

Journal of
Pulmonology and
Intensive Care

Review

DOI: 10.51271/JOPIC-0008

A current approach to acute mediastinitis

Sengül Üçer

Department of Infectious Diseases and Clinical Microbiology, Ankara Training and Research Hospital, University of Health Science, Ankara, Turkey

Cite this article: Üçer S. A current approach to acute mediastinitis. *J Pulmonol Intens Care.* 2023;1(2):38-41.

Corresponding Author: Sengül Üçer, sengulksm@hotmail.com

Received: 22/04/2023 ◆ **Accepted**: 09/05/2023 ◆ **Published**: 22/05/2023

ABSTRACT

Acute mediastinitis is still among the major causes of high mortality despite advances in antibiotic therapies, intensive care support, and novel diagnostic techniques. Mediastinitis may develop due to esophageal perforation, by a downward spread of neck infection, or after cardiothoracic surgery. While computed tomography is the most preferred imaging technique in diagnosis, broad-spectrum antibiotic therapy and surgical debridement are the mainstay of the treatment. It is essential to combine multiple interventions, such as appropriate antimicrobial prophylaxis, minimization of contamination, elimination of preoperative nasal *S. aureus* carriage, and the adoption of relevant surgical techniques, to prevent particularly postoperative mediastinitis.

Keywords: Acute mediastinitis, antibiotic therapy, surgical debridement

INTRODUCTION

Acute mediastinitis is a rare but severe and progressive condition characterized by diffuse inflammation in the mediastinum. The mediastinum is an anatomically closed intrathoracic cavity housing the heart, great vessels, trachea, esophagus, thymus, and lymph nodes. Due to the well-vascularized fat tissue in this space and the proximity of vital organs, advanced cases usually present with fever and tachycardia, accompanied by hypotension, multiple organ failure, rapid progression to sepsis, and the need for intensive care.[1,2]

Mediastinitis may develop due to esophageal perforation, by a downward spread from the neck (descending necrotizing mediastinitis (DNM)), or postoperatively (deep sternal surgical wound infection (DSWI) after sternotomy). At the same time, it can spread through the bloodstream from the pleural cavity or focus on infection in another region in the presence of empyema.[3]

EPIDEMIOLOGY, DEFINITIONS, AND RISK FACTORS

Acute mediastinitis is still among the major causes of high mortality despite advances in antibiotic therapies, intensive care support, and novel diagnostic techniques. The global mortality rate varies between 19-47% depending on the underlying cause. The condition is seen in both sexes but affects males one-sixth more. Its incidence increases in the third, fourth, and fifth decade of life, and advancing age contributes to mortality. About 60% of acute mediastinitis is due to complications following cardiac operations. While esophageal perforations account for 25-31% of mediastinitis, the remaining is mainly caused by oropharyngeal infection.[4]

POSTOPERATIVE MEDIASTINITIS

It is the condition in which the mediastinum becomes infected during DSWI following sternotomy. According to the Centers for Disease Control and Prevention (CDC), diagnosis is made upon fever >38.0°C, chest pain, purulent discharge in the surgical site in the presence of sternal instability, mediastinal widening in radiological imaging, microorganisms in fluid and tissue samples from the mediastinum, or histopathological classification of mediastinitis in tissue samples from the mediastinum.[5]

The sternal surgical wound infection is defined as a superficial infection when the infection affects the dermis and subcutaneous tissue or a DSWI when it extends below the sternum and anterior mediastinum. It was previously reported that DSWI occurs between 0.5% - 2.2% of patients following cardiac surgery and leads to 14% mortality. Intraoperative wound contamination from the patient's endogenous flora may be the most apparent factor for postoperative mediastinitis. The contamination occurs in almost all patients due to the prolonged time the sternotomy remains open during cardiac surgery. The degree, type, and host factors (nutrition, immunological status) of contamination determine the risk of infection. Providing that suitable conditions are ensured during surgery, the contamination causes infection in only a small number of patients.[6,7] The causative agent is usually monomicrobial, and what is isolated most prevalently is *Staphylococcus aureus*. Gram-negative bacilli, coagulase-negative staphylococci, and streptococci can also be detected as agents. Although surgical wound infection may occur months later in some cases, it emerges within the first 30 days postoperatively among the majority.

Preoperative, intraoperative, and postoperative risk factors for postoperative mediastinitis have already been defined. Preoperative risk factors are known to be nasal colonization with *Staphylococcus aureus*, diabetes mellitus (DM) or perioperative hyperglycemia, obesity, heart failure and left ventricular dysfunction, smoking, previous cardiac surgery, an end-stage renal disease requiring hemodialysis, chronic obstructive pulmonary disease, using an intra-aortic balloon pump, and using an electric razor instead of a razor blade for hair removal. While intraoperative risk factors are emergency surgery, using an internal mammary artery graft, prolonged perfusion and aortic clamp time, and prolonged surgical procedure (> 5 hours), postoperative risk factors are the need for mechanical ventilation, prolonged need for an intensive care unit, and poor glycemic control.[3,6,8-10]

DESCENDING NECROTIZING MEDIASTINITIS

DNM originates with direct extension of odontogenic (36-47%), pharyngeal (33-45%), and cervical (15%) infections from the deep facial, retropharyngeal, and peritracheal spaces to the tissue planes in the mediastinum. Its most prevalent sources are peritonsillar, parapharyngeal, dental, or odontogenic abscesses. In addition to prevalent infections (e.g., tonsillitis, epiglottitis, pharyngitis), it can also emerge due to primary neck infections, cervical lymphadenitis, suppurative thyroiditis, parotitis, and traumatic endotracheal intubation. The retropharyngeal space opens directly into the posterior mediastinum, accounting for the spread of 70% of oropharyngeal infections. If not treated early and appropriately, it may cause multiple organ failure, sepsis, and mortality (11-40%). Normal flora members of the oral cavity, upper respiratory tract, and ear mucosal surfaces are responsible for the infection; thus, it is typically polymicrobial. On the other hand, the most prevalently isolated agents are known to be *Streptococcus* spp., *S. aureus*, and anaerobes (*Peptostreptococcus* spp., *Fusobacterium nucleatum*, *Prevotella* spp.). In addition to these pathogens, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* may be causative agents in autogenic or sinus-borne infections.[4] Diagnostic criteria proposed by Estrera et al.[11] include clinical signs of severe infection, characteristic findings on radiological imaging, intraoperative or postmortem detection of necrotizing mediastinal infection, and a relationship between necrotizing mediastinitis and oropharyngeal or cervical infection. Immunosuppression, DM, oral glucocorticoids, peripheral arterial disease, and reduced tissue oxygenation due to cardiac and respiratory failure are major risk factors for DNM.

MEDIASTINITIS FOLLOWING ESOPHAGEAL PERFORATION

The passage of colonized microorganisms, salivary, esophageal, and gastric contents into the mediastinum due to any disruption of the esophageal wall integrity results in mediastinitis. More than half of esophageal perforations occur iatrogenically during endoscopic procedures. While this probability may be negligible during simple endoscopy (< 0.5%), it increases (2-6%) when performing dilatation or using a rigid esophagoscope for achalasia. Perforation is more likely in sites with physiological stenosis (e.g., the cricopharyngeal muscle and esophagogastric junction). Spontaneous perforation (Boerhaave's syndrome) accounts for up to 15% of all perforations, and such patients usually have a history of alcoholism and/or gastric and duodenal ulcers. Its other less prevalent causes are trauma, surgical anastomosis, and malignancy.[12,13] The agents in mediastinitis following esophageal perforation are the members of the normal oropharynx flora (streptococci, anaerobes, *Neisseria* spp., *Haemophilus* spp.); nevertheless, the patient's immunosuppression, intubation, enteral nutrition, and recent antibiotic exposure may change this profile. In these cases, the flora members are replaced by gram-negative bacteria, *S. aureus*, and *Candida* spp., and it is expected that these microorganisms will emerge as agents.[14]

CLINICAL MANIFESTATIONS

The clinical findings of mediastinitis vary by the underlying cause; fever, chills, and tachycardia are usual findings of mediastinitis. Pain can be masked, particularly among intensive care patients, and throat infection and trismus may accompany the clinical picture. Moreover, symptoms of systemic inflammatory response syndrome (SIRS) may be observed depending on the underlying etiology and patient characteristics. Increased inflammatory parameters in laboratory tests and elevated leukocyte count, C-reactive protein, and procalcitonin levels are also prevalent. Thrombocytopenia or disseminated intravascular coagulation may develop in association with sepsis. For appropriate antimicrobial therapy, fluid and tissue samples from the infected sternum or mediastinum during surgical debridement or abscess and blood cultures may need to be requested. Pleural fluid and bronchoalveolar lavage samples may also be required in patients in advanced stages. Superficial wound cultures should be carefully evaluated as they can be an indicator of colonization.

RADIOLOGICAL IMAGING

A simple posteroanterior chest radiograph may demonstrate the presence of air between the sternal edges. The displacement of one or more sternal wires may be an indirect indication of separation of the sternum.[15] Computed tomography (CT) should be performed on the neck and chest to confirm the diagnosis. In addition to being rather sensitive for diagnosis, CT can also provide insights about the underlying cause and the extent of the infection, helping plan appropriate surgical intervention. Sternal separation on CT, the presence of free air under the sternum, and mediastinal fluid collections indicate the presence of mediastinitis. Despite the high sensitivity, a differential diagnosis may not be possible in postsurgical mediastinitis because of postoperative inflammatory changes. In this case, repeat CT or scintigraphy may be needed to assess progression.[16]

TREATMENT

Relevant empirical antibiotic therapy should be initiated as soon as after collecting blood samples, and current surgical techniques should be considered in patients with suspected or diagnosed mediastinitis. Control of the focus of infection

and surgical debridement are the mainstay of the treatment. Clinical progression may vary depending on rapid diagnosis, adequate treatment, underlying cause, and comorbidities.[17]

Broad-spectrum intravenous antibiotic therapy should be initiated in mediastinitis associated with a sternal surgical wound infection after collecting cultures for microbiological identification and antibiogram. Empirical antibiotic therapy should include methicillin-susceptible *S. aureus*, skin flora members, and gastrointestinal gram-negative bacteria. Since methicillin-resistant coagulase-negative staphylococci and MRSA are prevalent in addition to broad-spectrum beta-lactam penicillin (e.g., piperacillin-tazobactam), vancomycin should be added in the treatment until obtaining culture results. Treatment should be planned for two-six weeks by evaluating adequate debridement and osteomyelitis.

Many different approaches have been described in the surgical treatment of post-sternotomy mediastinitis: reconstruction with revision (with open dressing), primary closure, closed irrigation, negative pressure wound therapy, and reconstruction with vascularized soft tissue (omentum, pectoral muscle) flap. Despite no consensus on the most appropriate surgical approach, there is at least some agreement on the necessity of wound debridement. Primary closure and tertiary closure or delayed primary closure are the two most commonly preferred techniques of wound closure. The wound is left open for follow-up and treatment following debridement and closed after a few days.[3]

Broad-spectrum intravenous antibiotic therapy, including aerobic and anaerobic bacteria, should be started for DNM. Intensive care monitoring may be required for optimal treatment in the presence of severe sepsis or septic shock. After treatment of the pharyngeal or dental focus and airway management, rapid and adequate neck and mediastinal drainage should be performed. Airway compression due to inflammation and edema is prevalent, and early tracheotomy ensures airway safety. Rapid surgical intervention, including systematic debridement and opening of the fascial spaces, is required to prevent the severe complications of persistent and progressive disease.[18] The surgical strategy is decided on by the extent of the disease. While cervicectomy and transcervical drainage may be adequate for localized infections in the upper mediastinum (above the carina), additional subxiphoid drainage should be considered in localized disease and stable cases where the infection progresses downward. More aggressively, median sternotomy and complete removal of necrotic tissue may also be required. Although posterolateral thoracotomy is acknowledged as a standard approach, the posterior mediastinum can be accessed in selected patients with the help of the clamshell approach, uni/bilateral thoracotomy, or uni/bilateral video-assisted thoracoscopic surgery (VATS). Yet, re-operation rates were previously reported to be high in research where less invasive approaches, such as subxiphoid drainage and VATS, were adopted. As a rule of thumb, the optimal treatment is radical surgical debridement of the affected tissue (e.g., pericardial adipose tissue and thymus) with an open thoracic approach.[19] Overall, each method bears potential pros and cons. Therefore, the surgical approach should be carefully chosen by the patient's condition, the extent of the disease, and the surgeon's experience to reduce the rates of complications, re-operation, and mortality.[19,20] The patient's oral intake should be discontinued, and aggressive intravenous fluid replacement and broad-spectrum antibiotic therapy covering aerobic and anaerobic bacteria should be started in mediastinitis developing due to esophageal peroration. Antifungal coverage may be required in immunosuppressive patients or those with prior broad-spectrum antibiotic use. The treatment should be assisted with proton pump inhibitors to prevent acid reflux. Planning an optimal treatment may require a multidisciplinary approach considering the patient's condition and the dynamics of the esophageal perforation.[21,22]

Primary repair of the perforation site is required in all cases, but the repair is more likely to be disrupted in patients diagnosed after 72 hours. Yet, the repair may not be convenient for patients with invisible or inaccessible cervical perforations, diffuse mediastinal necrosis or perforations that cannot be approximated, esophageal malignancies, end-stage achalasia, or clinical instability.[23]

Non-operative Approach

It can be preferred in minor iatrogenic or traumatic injuries with minimal extraluminal contamination, usually diagnosed at the time of perforation during or shortly after the procedure. The most critical aspect of the non-operative approach is careful patient selection. Iatrogenic cervical perforations are often deemed suitable for non-operative management. Endoscopic stent placement/vacuum-assisted closure and percutaneous or surgical intervention may be necessary for larger leaks.[24]

Prophylaxis

In the perioperative period, it is often aimed to minimize contamination and optimize the immune response in any applications to prevent surgical wound infection. Preoperative screening for nasal carriage of MRSA should be adopted to avoid virulent pathogen contamination. A five-day topical mupirocin treatment is recommended for the elimination of carriage. A single dose of beta-lactam antibiotic should be administered for cardiac surgical antibiotic prophylaxis in areas with a low incidence of MRSA. For beta-lactam allergy, prophylaxis may need to be ensured with vancomycin. While cefazolin should be given within 60 minutes of skin incision, vancomycin should be administered as an infusion for at least one hour. Nevertheless, antibiotic prophylaxis should not be applied for longer than 48 hours in the postoperative period. Skin antisepsis and perioperative hyperglycemia control should be ensured with povidone-iodine or chlorhexidine gluconate.[25]

Careful median sternotomy, bleeding control, and limited dissection are necessary to prevent infection during the operation. Paramedian sternotomy is associated with postoperative sternal instability. Sternal instability and dissociation may be an indication of surgical wound infection and may also end up with bacterial overgrowth. Rigid mechanical fixation of the sternal edges reduces the infection rate. Many novel techniques (e.g., surgical plate, wire) are utilized, but prospective controlled research is needed to demonstrate that these methods can reduce the rate of mediastinitis. When comparing the use of the bilateral internal mammary artery (BIMA) with the use of only the left internal mammary artery (LIMA), it was previously reported that the use of BIMA reduces the vascularization of the sternum and increases the risk of surgical wound infection. However, the subsequent research concluded that the increase in this rate is often significant in diabetic patients. Skeletonized IMA dissection is recommended in the case of DM or when BIMA is utilized.[26-28]

CONCLUSION

Acute mediastinitis is a clinical condition with a high mortality rate mostly occurs as a complication of a cardiothoracic surgical procedures.Prevention of surgical site infection depends on compliance with infections control measures and appropriate surgical intervention. Rapid diagnosis and eligible treatment approach should be implemented for reducing mortality.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Palma DM, Giuliano S, Cracchiolo AN, et al. Clinical features and outcome of patients with descending necrotizing mediastinitis: prospective analysis of 34 cases. *Infection*. 2016;44(1):77-84. doi:10.1007/s15010-015-0838-y
2. Biancari F, D'Andrea V, Paone R, et al. Current treatment and outcome of esophageal perforations in adults: systematic review and meta-analysis of 75 studies. *World J Surg.* 2013;37(5):1051-1059. doi:10.1007/s00268-013-1951-7
3. Abu-Omar Y, Kocher GJ, Bosco P, et al. European Association for Cardio-Thoracic Surgery expert consensus statement on the prevention and management of mediastinitis. *Eur J Cardiothorac Surg.* 2017;51(1):10-29. doi:10.1093/ejcts/ezw326
4. Ridder GJ, Maier W, Kinzer S, Teszler CB, Boedeker CC, Pfeiffer J. Descending necrotizing mediastinitis: contemporary trends in etiology, diagnosis, management, and outcome. *Ann Surg.* 2010;251(3):528-534. doi:10.1097/SLA.0b013e3181c1b0d1
5. Centers for Disease Control and Prevention. CDC/NHSN surveillance definitions for specific types of infections. https://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf (Accessed on April 10, 2017)
6. Perrault LP, Kirkwood KA, Chang HL, et al. A Prospective Multi-Institutional Cohort Study of Mediastinal Infections After Cardiac Operations. *Ann Thorac Surg.* 2018;105(2):461-468. doi:10.1016/j.athoracsur.2017.06.078
7. Filsoufi F, Castillo JG, Rahmanian PB, et al. Epidemiology of deep sternal wound infection in cardiac surgery. *J Cardiothorac Vasc Anesth*. 2009;23(4):488-494. doi:10.1053/j.jvca.2009.02.007
8. Risnes I, Abdelnoor M, Almdahl SM, Svennevig JL. Mediastinitis after coronary artery bypass grafting risk factors and long-term survival. *Ann Thorac Surg.* 2010;89(5):1502-1509. doi:10.1016/j.athoracsur.2010.02.038
9. Friedman ND, Bull AL, Russo PL, et al. An alternative scoring system to predict risk for surgical site infection complicating coronary artery bypass graft surgery. *Infect Control Hosp Epidemiol.* 2007;28(10):1162-1168. doi:10.1086/519534
10. Tanner J, Norrie P, Melen K. Preoperative hair removal to reduce surgical site infection. *Cochrane Database Syst Rev.* 2011;(11):CD004122. doi:10.1002/14651858.CD004122.pub4
11. Estrera AS, Landay MJ, Grisham JM, Sinn DP, Platt MR. Descending necrotizing mediastinitis. *Surg Gynecol Obstet.* 1983;157(6):545-552.
12. Ryom P, Ravn JB, Penninga L, et al. Aetiology, treatment and mortality after oesophageal perforation in Denmark. *Dan Med Bull.* 2011;58(5):A4267.
13. Brinster CJ, Singhal S, Lee L, Marshall MB, Kaiser LR, Kucharczuk JC. Evolving options in the management of esophageal perforation. *Ann Thorac Surg.* 2004;77(4):1475-1483. doi:10.1016/j.athoracsur.2003.08.037
14. Norder Grusell E, Dahlén G, Ruth M, et al. Bacterial flora of the human oral cavity, and the upper and lower esophagus. *Dis Esophagus*. 2013;26(1):84-90. doi:10.1111/j.1442-2050.2012.01328.x
15. Graeber GM, McClelland WT. Current concepts in the management and reconstruction of the dehisced median sternotomy. *Semin Thorac Cardiovasc Surg.* 2004;16(1):92-107. doi:10.1053/j.semtcvs.2004.01.008
16. Exarhos DN, Malagari K, Tsatalou EG, et al. Acute mediastinitis: spectrum of computed tomography findings. *Eur Radiol.* 2005;15(8):1569-1574. doi:10.1007/s00330-004-2538-3
17. Falagas ME, Tansarli GS, Kapaskelis A, Vardakas KZ. Impact of vacuum-assisted closure (VAC) therapy on clinical outcomes of patients with sternal wound infections: a meta-analysis of non-randomized studies. *PLoS One*. 2013;8(5):e64741. doi:10.1371/journal.pone.0064741
18. Sandner A, Börgermann J. Update on necrotizing mediastinitis: causes, approaches to management, and outcomes. *Curr Infect Dis Rep.* 2011;13(3):278-286. doi:10.1007/s11908-011-0174-z
19. Kiernan PD, Hernandez A, Byrne WD, et al. Descending cervical mediastinitis. *Ann Thorac Surg.* 1998;65(5):1483-1488. doi:10.1016/s0003-4975(98)00142-8
20. Singhal P, Kejriwal N, Lin Z, Tsutsui R, Ullal R. Optimal surgical management of descending necrotising mediastinitis: our experience and review of literature. *Heart Lung Circ.* 2008;17(2):124-128. doi:10.1016/j.hlc.2007.08.004
21. Abbas G, Schuchert MJ, Pettiford BL, et al. Contemporaneous management of esophageal perforation. *Surgery.* 2009;146(4):749-756. doi:10.1016/j.surg.2009.06.058
22. Ben-David K, Behrns K, Hochwald S, et al. Esophageal perforation management using a multidisciplinary minimally invasive treatment algorithm. *J Am Coll Surg.* 2014;218(4):768-774. doi:10.1016/j.jamcollsurg.2013.12.033
23. Salo JA, Isolauri JO, Heikkilä LJ, et al. Management of delayed esophageal perforation with mediastinal sepsis. Esophagectomy or primary repair?. *J Thorac Cardiovasc Surg.* 1993;106(6):1088-1091.
24. Vogel SB, Rout WR, Martin TD, Abbitt PL. Esophageal perforation in adults: aggressive, conservative treatment lowers morbidity and mortality. *Ann Surg.* 2005;241(6):1016-1023. doi:10.1097/01.sla.0000164183.91898.74
25. Engelman R, Shahian D, Shemin R, et al. The Society of Thoracic Surgeons practice guideline series: Antibiotic prophylaxis in cardiac surgery, part II: Antibiotic choice. *Ann Thorac Surg.* 2007;83(4):1569-1576. doi:10.1016/j.athoracsur.2006.09.046
26. Itagaki S, Cavallaro P, Adams DH, Chikwe J. Bilateral internal mammary artery grafts, mortality and morbidity: an analysis of 1 526 360 coronary bypass operations. *Heart.* 2013;99(12):849-853. doi:10.1136/heartjnl-2013-303672
27. Deo SV, Shah IK, Dunlay SM, et al. Bilateral internal thoracic artery harvest and deep sternal wound infection in diabetic patients. *Ann Thorac Surg.* 2013;95(3):862-869. doi:10.1016/j.athoracsur.2012.11.068
28. Bryan CS, Yarbrough WM. Preventing deep wound infection after coronary artery bypass grafting: a review. Tex Heart Inst J. 2013;40(2):125-139.

Journal of
Pulmonology and
Intensive Care

Review

DOI: 10.51271/JOPIC-0009

An overview of the concept of medical intervention and informed consent according to Turkish law

Ramazan Baldemir

Department of Anesthesiology and Reanimation, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkey

Cite this article: Baldemir R. An overview of the concept of medical intervention and informed consent according to Turkish law. *J Pulmonol Intens Care.* 2023;1(2):42-45.

Corresponding Author: Ramazan Baldemir, baldemir23@yahoo.com

Received: 25/04/2023 ◆ **Accepted**: 09/05/2023 ◆ **Published**: 22/05/2023

ABSTRACT

Medical intervention refers to any action taken against the physical and mental structure of the person for the purpose of treatment by an authorized person in the medical field. Medical interventions without legal compliance conditions constitute a crime legally. In order for the intervention to be lawful; The person performing the medical intervention must be a physician, there must be the necessary indication for medical intervention, the patient must have informed consent, and the physician must perform a meticulous medical intervention in accordance with the requirements of medical science. According to our constitution, people have the right to determine their own future. Therefore, the physician must obtain the consent of the patient before intervening in the patient's bodily integrity. The aim of the physician to heal the patient does not give any privilege to the physicians in this regard. According to the legislation, it can be stated that it is more appropriate to make the enlightenment verbally, but it would be more beneficial to put the verbal clarification in writing in terms of proof of the clarification. In order for the patient's consent to be valid, the patient must have a good grasp of the subject to which he or she gave consent. For this reason, the patient should be fully illuminated.

Keywords: Medical intervention, law, informed consent, consent,

INTRODUCTION

In order to diagnose and treat the diseases, some examinations are performed on the patients, treatment is planned for the diagnosis made as a result of the examinations, and some interventions are made to the patients.[1] In this case, we come across the concept of medical intervention. It is very important for physicians to know the legal dimension of their medical interventions. Medical interventions are considered as a violation of bodily immunity from a legal point of view, as well as an intervention in private life.[2,3] In this case, "why are not all physicians held legally responsible for their medical interventions and prosecuted?" the question comes to our mind. We can say that the reason for this is that the intervention is made in accordance with the law. Physicians can defend themselves better and feel safer only when they are sure that their medical intervention is legal.[4] In this article, it is aimed to talk about the legal dimension of the concept of medical intervention, the conditions required for the medical intervention to be legal, and the concept of informed consent, which is based on the literature data and the opinions in the doctrine.

THE CONCEPT OF MEDICAL INTERVENTION

Medical intervention refers to any action taken against the physical and mental structure of the person for the purpose of treatment by an authorized person in the medical field, according to the patient rights regulation and biomedicine agreement.[5-7] The main purpose of medical interventions is limited to correcting the deterioration in the physical and mental structure of the person. However, studies such as plastic surgery, sterilization, vaccination, and population planning, which are not for treatment purposes and are performed based on the consent of the person, are also considered medical interventions.[8]

LEGAL DIMENSION OF THE CONCEPT OF MEDICAL INTERVENTION AND LEGAL COMPLIANCE REQUIREMENTS

There is a consensus in Turkish Law that any medical intervention by a physician such as medication, psychotherapy, and surgery is "injury".[3] In addition, medical interventions mean a violation of bodily immunity from a legal point of view, as well as an intervention in private life according to the European Court of Human Rights.[2,3] For this reason, medical interventions that do not comply with the law may be criminal offenses, and physicians may be liable for compensation for this reason.[2] For this reason, it is important to ensure compliance with the law in order to avoid liability for the physician. However, in case of legal

compliance reasons, medical intervention turns into a lawful action.[9] The reasons for compliance with the law are expressed in many national and international regulations such as the Constitution, laws, regulations, statutes, and treaties.[2] Article 17 of the Constitution of the Republic of Turkey states that "Everyone has the right to live and to protect and develop their material and spiritual existence. Except for medical obligations and the cases are written in the law, the body integrity of the person cannot be touched; cannot be subjected to scientific and medical experiments without his consent." it is called. According to the first 4 articles of the Law on the Execution of Medicine and Medical Arts, the person performing the medical intervention must be a physician, again, Article 70 of the same law, Article 6 of the Law on Organ and Tissue Removal, Storage, and Transplantation, Article 4 of the Law on Population Planning, Article 5 of the Biomedicine Convention and According to Article 5 of the Patient Rights Regulation, informed consent is required.[3] Accordingly, in order for the medical intervention to be in accordance with the law; **1**- the person performing the medical intervention must be a physician, **2**- the necessary indication for the medical intervention must be present, **3**- the informed consent must be present, and **4**- the physician must perform a meticulous medical intervention in accordance with the requirements of medical science.[3] It is also important which of the conditions of compliance with the law are fulfilled in the distinction of whether the legal responsibility of the physician is the result of intentional or negligent action. According to Hakeri, in the absence of the first three conditions, liability will arise due to an intentional action on the part of the medical responder, while only in the absence of the last condition, liability due to the negligence is mentioned.[3]

INFORMED CONSENT

Informed consent, which is one of the conditions of legality is one of the important issues that physicians should pay attention to. The right to determine one's own future is guaranteed by Article 17 of our constitution. Therefore, the physician must obtain the patient's consent before intervening in the patient's bodily integrity.[3] The aim of the physician to heal the patient does not give any privilege to the physicians in this regard.[3] This shows us that the patient's wish, which is decided with free will, comes before the patient's well-being.[3] However, in order for the patient's consent to be valid, proper illumination is essential. Otherwise, the validity of the given consent is not mentioned.[3] Even if the medical intervention is performed by the physician in accordance with all the rules and is successful, the physician may be held responsible in terms of criminal law.[3] Despite this, it is thought that there is a lack of information in health institutions and physicians about the importance of informed consent, in other words, informed consent, and they should be informed in terms of ethical and legal obligations.[10]

The clarification process to be made to the patient or patient's relatives and the informed consent forms to be signed should be in an understandable language, in an understandable language, in accordance with the social and cultural level of the other party, taking into account the education level of the other party, and should be easily readable.[1,10,11] In order for the patient to decide on medical intervention in an enlightened and conscious manner, she/he must have sufficient information about the medical intervention and its details.[12] In this context, the patient should be informed verbally, in writing, and, if necessary, using various visuals. This information should include titles such as the reasons for the medical intervention, the benefits it will provide, the harms it may cause, other intervention methods, and the situations that may be caused by not applying the intervention.[13] The most detailed provisions on this subject are included in the patient rights regulation. According to this; the patient's disease and the causes of the disease, how the disease will continue, the content of the medical intervention to be performed, who will perform this intervention, how the intervention will be performed, how long the intervention will take, other intervention options, if any, the benefits and harms of the intervention options, the risks and complications that may be encountered, information such as the important characteristics of the drugs to be used, the lifestyle recommendations that are critical for the patient's health, and how to reach medical help on the same issue when necessary, and the situations that the patient will encounter if he/she does not accept the intervention should be explaned to the patient.[10,14] In addition, the patient may be harmed due to the side effects of the drugs to be used for treatment. It is up to the physician to explain all these possibilities in a way that the patient can understand and to enable the patient to make a free decision.[15,16] It is also very important to answer the patient's questions. It is also important that the patient is in a position to make a decision after adequate information in terms of both ethics and law.[10] It is important that the patient has the power to discriminate and makes the decision of acceptance or rejection voluntarily.[17] If the patient has legal capacity, informed consent must be obtained from the patient, and if the patient is not in a position to give consent or does not have legal capacity, it should be obtained from her legal representative.[1]

Although it is stated that obtaining informed consent in written form will make it easier for the patient to understand the information given, it is stated in the patient rights regulation that the enlightenment should be made verbally, and it is more appropriate to give verbal information from the legal point of view.[10]

As a rule, the physician who will perform the medical intervention should fulfill the obligation to enlighten.18 However, if it is obligatory for different people to carry out the informing and intervention, this should be explained to the patient. In this case, it should be clarified by a physician who has the ability to inform.[14,19] If the physician who will do the intervention will not be able to inform, it is important that the physician who will do the informing instead of that physician has a good command of the subject. In addition, the physician who will perform the intervention should make sure that the informing is done.[14,20]

Health professionals other than physicians should also inform about the medical interventions they are authorized. For example, a physiotherapist should tell the patient about the risks that may develop due to the exercises he will perform.[14,21]

Informing should be done to the patient herself/himself. The severity of the disease or the fact that the patient's psychology may be adversely affected does not change this rule. Informing the spouse, son or other relatives of the patient does not make the consent valid.[14,18] If the patient does not have the power to distinguish, the guardian or guardian is informed. In the case of a small and limited patient who has the power to discriminate, both the patient himself and

his parent or guardian should be informed.[22] However, it would be more appropriate to inform the child in a way that the child can understand.[14]

The patient should be given a reasonable period of time, except for emergencies, so that she can research and make a healthy decision about the medical intervention or alternatives to be applied after the information given to her/him.[14] Under the European Statute on Patients' Rights, it is stated that information should be given at least 24 hours before the medical intervention.[16] Especially in major surgical interventions, attention should be paid to informing 24 hours before the surgery as a rule, and informing the evening before the surgical intervention should be avoided.[14]

Care should be taken to ensure that the information to be provided is personal to the patient. This method should not be preferred since the previously prepared printed information cannot sufficiently inform the patient.[16] While informing the patient, audio and video recordings can be taken by informing the patient.[14] In a decision of the Council of State, it has been stated that the information document prepared in a printed way is not a valid information due to the lack of details of the treatment to be applied, possible side effects, what are the expected benefits with the treatment, complications, alternative treatments and the risks that may occur in case of rejection of the treatment.[23] The Court of Cassation did not consider the form prepared in print as informative with similar decisions.[24,25]

INFORMED CONSENT IN MINORS WHO DO NOT HAVE THE CAPACITY TO CONSENT

Since the legal representative is the parents for the minors who do not have the capacity to consent, both parents must give the consent together. If the parents cannot make a joint decision on giving consent, a court decision should be taken, taking into account the best interests of the child. If there is a suspicion that the parents are preventing the child's treatment, the judge can also decide on their own.[26] In emergencies, the physician can decide for himself, which is very beneficial for the child, but if it is not urgent and the indication is controversial, it is important to obtain the consent of the parents. The decision should be made taking into account the danger situation of the minor.[27] If the parents of the minor are divorced, the authority to give consent belongs to the party holding the custody of the child.[14]

SUPREME COURT DECİSİONS AND INFORMED CONSENT

Courts give particular importance to the informing phase when making decisions. The Court of Cassation declared the expert report that did not mention the issue of informing and consent invalid in one of its decisions. Also considered the expert's failure to examine whether or not the informing was made as an incomplete examination and research, and concluded that a judgment could not be made in this way.[28]

In the decisions of the Council of State and the Supreme Court, it is stated that it is not sufficient to just have the consent document signed, it is necessary to inform the person verbally, and the information and document that the patient has been informed should be included in the file.[29,30] Again, in a decision taken by the Council of State, it was stated that it was necessary to investigate whether detailed information was given about complications since a consent document that was not fully read by the patient was signed by the patient.[31] In a decision of the Court of Cassation, it was stated that the risks of the treatment method for the health of the patient, the use of the given drugs, and possible side effects should be clarified. In addition, he did not consider it sufficient to be aware of side effects and complications in general terms. Considered it necessary to explain what kind of complications the surgery had.[32]

According to an opinion, it was stated that it is not necessary to explain the risks that may occur with all their possibilities, and it was stated that it would be appropriate to describe the risks by drawing a general framework.[14,16] However, the Supreme Court ruled that the consent obtained was invalid on the grounds that there was no indication in a decision that the physician directed the patient to a treatment with less complication probability.[33]

A point that should be given importance; The fact that the patient's consent at the stage of the medical intervention contract does not mean that the patient consents to all subsequent interventions. Informed consent should be obtained from the patient again, taking into account the changing conditions during the treatment phase.[34] It should not be understood that the patient consented to all the interventions to be applied during the treatment process based on his/her initial will.[34] However, these decisions have been criticized by some authorities as they impose a wide disclosure obligation on physicians for all kinds of medical interventions.[14]

Another point to be considered is; patient consent alone is not sufficient in terms of the legality of medical intervention. The physician cannot apply everything that the patient consents to the patient. It cannot apply an intervention that does not have an indication, only at the request of the patient.[3] In this case, the physician will be responsible for the absence of an indication, even if the patient consents.

CONCLUSION

As a result, in the absence of compliance with the law, medical interventions performed by physicians while performing their profession constitute a crime in terms of law. For this reason, it is very important for physicians to know the necessary conditions for the medical intervention to be in compliance with the law, to have a good command of the legislation related to their profession, and to act accordingly. In order for the intervention to be lawful; The person performing the medical intervention must be a physician, there must be the necessary indication for medical intervention, the patient must have informed consent, and the physician must perform a meticulous medical intervention in accordance with the requirements of medical science. Among these conditions, sensitivity should be shown by taking into account the judicial decisions regarding the issue of informed consent.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Oruç MA, Şahin B, Demirkılıç F, Keskin Göksel A, Büyükkarabacak HY. Girişimsel İşlemler Öncesi İmzalatılan Aydınlatılmış Onam Formları İle İlgili Hasta Algı Düzeyinin Belirlenmesi. *Eurasian Journal Of Health Technology Assessment*. 2022; 6(2): 90-101. doi: 10.52148/ehta.1134950
2. Aslan S. Tıbbi müdahalelerin hukuka uygunluk şartları. Master's Thesis. İnönü Üniversitesi Sağlık Bilimleri Enstitüsü. 2022.
3. Hakeri H. Tıp Ceza Hukuku. 3rd ed. Ankara, Seçkin Yayıncılık; 2023
4. Can HY, Yiğit Y, Yüzbaşıoğlu E. (2022). Göz Kliniğinde Uygulanan Aydınlatılmış Onam Formları Yeterli mi?. *Adli Tıp Bülteni*. 2022;27(2):157-161
5. Şeker Z, Özesen TA, Kaya K, Çekin N. Hatalı tıbbi uygulama iddiası ile açılan davalarda aydınlatılmış onam ile ilgili yargıtay kararlarının değerlendirilmesi: kesitsel araştırma. *Turkiye Klinikleri J Foren Sci Leg Med*. 2023;20(1):11-23
6. Kıcalıoğlu M. Yargı kararları ışığında doktorun (hekimin) tıbbi müdahaleden doğan hukuki sorumluluğu. *Terazi Hukuk Dergisi*. 2006; 1(4): 13-9.
7. Ayan M. Tıbbi Müdahalelerden Doğan Hukuki Sorumluluk, Ankara, Kazancı Hukuk Yayınları; 1991: 5-113.
8. Dural M, Öğüz T, Sarı S. Türk Özel Hukuku Cilt II Kişiler Hukuku, İstanbul, Filiz Kitabevi; 2015: 82-108.
9. Eren F. Borçlar Hukuku Genel Hükümler, 19. Baskı, Ankara, Yetkin Yayınları; 2015
10. Alkan OG, Sert G. Informed Consent Awareness and Practıces of the Physicians Before Medical Intervention. *Türkiye Biyoetik Dergisi*. 2022; 9(4): 146-154
11. Ebem E, Tutar MS, Yıldız M, Canıtez A, Kara Ö, Kozanhan B. İntravenöz ve İntramüsküler Enjeksiyon Bilgilendirilmiş Onam Formlarının Okunabilirlik Açısından Değerlendirilmesi. *Anatolian Clinic the Journal of Medical Sciences*. 2019; 24(2): 132-136.
12. Petridis G, Güven AT, Kalfoglou S, Özcan ŞŞ. Informed Consent in Forensic Genetics. *Journal of Medical Sciences*. 2023; 4(2): 62-67.
13. Sert G. Uluslararası Bildirgeler ve Tıp Etiği Acısından Hasta Hakları. Seckin Yayınları; 2019
14. Öz AK. Tıbbi müdahalelerde aydınlatılmış onam (rıza) kavramının geçerliliğinin tartışılması ve Danıştay ve Yargıtay kararları ışığında değerlendirilmesi. Master's Thesis. Bakırçay Üniversitesi Lisansüstü Eğitim Enstitüsü. 2022.
15. Özdemir H. Hekimin Hukuki Sorumluluğu. *Erciyes Üniversitesi Hukuk Fakültesi Dergisi*. 2016; 11(1), 33-81.
16. Hakeri H. Tıp Hukuku-Genel Hükümler. 25 th ed. Ankara, Seçkin Yayıncılık; 2022
17. Erdoğan N, Kara M, Hızal A, Hızal Arslan S . Aydınlatılmış Onam: Uygulama ve Tıp Hukuku Acısından Sorunlar. *Erciyes Tıp Dergisi*. 2011;33(2):165-170
18. Aykın, AC, Çınarlı S. Sağlık Personelinin Hukuki Sorumluluğu Ankara, Seçkin Yayınları;2016
19. Erman B. Ceza Hukukunda Tıbbi Müdahalelerin Hukuka Uygunluğu. Ankara, Seçkin Yayıncılık; 2003
20. Serel TA. Cerrahi Branşlarda Bilgilendirilmiş Rıza. In Yılmaz N, Özcengiz D, eds. Bilgilendirilmiş Rıza. Ankara, Yetkin Yayınları; 2020: 279-289.
21. Subaşı İ. Hekimin Aydınlatma Yükümlülüğü-Aydınlatılmış Onam-Tazminat Sorumluluğu. Ankara, Şeçkin Yayıncılık;2016
22. Altun A. Küçüğün Tıbbi Müdahaleye Rızası. *Necmettin Erbakan Üniversitesi Hukuk Fakültesi Dergisi*. 2018; 37-52.
23. Danıştay 15. Dairesi'nin 20.12.2018 Tarihli ve 2016/2055 Esas ve 2018/8407 Karar sayılı kararı. Available from: https://karararama.danistay.gov.tr/
24. Yargıtay 13. Hukuk Dairesi'nin 21.12.2016 Tarihli ve 2015/32882 Esas ve 2016/24003 Karar sayılı kararı, Available from: https://karararama.yargitay.gov.tr/
25. Yargıtay 13. Hukuk Dairesi'nin 25.11.2013 Tarihli ve 2013/1737 Esas ve 2013/29148 Karar sayılı kararı, Available from: https://karararama.yargitay.gov.tr/
26. Serozan R. Çocuk Hukuku. İstanbul, Vedat Kitapçılık; 2017
27. İmamoğlu SH. Çocuğun Kişiğinin Ana Babaya Karşı Korunması. *Ankara Üniversitesi Hukuk Fakültesi Dergisi*. 2005; 54(2)ı183-218.
28. Yargıtay 13. Hukuk Dairesi'nin 18.09.2008 tarihli ve 2008/4519 Esas ve 2008/10750 Karar sayılı kararı , Available from: https://karararama.yargitay.gov.tr/
29. Yargıtay 13. Hukuk Dairesi'nin 04.07.2018 Tarihli ve 2016/25663 Esas ve 2018/7615 Karar sayılı kararı, Available from: https://karararama.yargitay.gov.tr/
30. Danıştay 10. Dairesi'nin 18.10.2021 Tarihli ve 2019/6882 Esas ve 2021/4854 Karar sayılı kararı, Available from: https://karararama.danistay.gov.tr/
31. Danıştay 10. Dairesi'nin 18.11.2021 Tarihli ve 2019/6841 Esas ve 2021/5618 Karar sayılı kararı, Available from: https://karararama.danistay.gov.tr/
32. Yargıtay 13. Hukuk Dairesi'nin 09.04.2014 Tarihli ve 2013/30822 Esas ve 2014/10772 Karar sayılı kararı, Available from: https://karararama.yargitay.gov.tr/
33. Yargıtay 12. Ceza Dairesi'nin 20.01.2015 tarihli ve 2014/7841 Esas ve 2015/710 Karar sayılı kararı, Available from: https://karararama.yargitay.gov.tr/
34. Şenocak Z. Küçüğün tıbbi müdahaleye rızası. *Ankara Üniversitesi Hukuk Fakültesi Dergisi*, 2001, 50(4): 65-80.

Journal of
Pulmonology and
Intensive Care

Case Report

DOI: 10.51271/JOPIC-0005

Lung cancer in a welder; case report

Serhat Özgün[1], Gülden Sarı[1], Adem Koyuncu[1], Ceprail Şimşek[1], Funda Demirağ[2]

[1]Department of Occupational Diseases Training, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkey
[2]Department of Pathology, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkey

Cite this article: Özgün S, Sarı G, Koyuncu A, Şimşek C, Demirağ F. Lung cancer in a welder; case report. *J Pulmonol Intens Care.* 2023;1(2):46-48.

Corresponding Author: Serhat Özgün, serhatozgun@hotmail.com

Received: 17/04/2023 ◆ **Accepted**: 27/04/2023 ◆ **Published**: 22/05/2023

ABSTRACT

There are more than one million deaths due to lung cancer every year. Occupational exposure is thought to be responsible for 10% of lung cancer cases. A 51-year-old male patient applied to our clinic with complaints of weakness and rapid fatigue that have been going on for 1 month. In his professional history, it was learned that he has been working as welder for 24 years. On the thoracic computed tomography, a nodular lesion of approximately 5 cm in size with irregular borders and approximately 1.7 cm in size with irregular borders in the anterior left upper lobe, surrounding the hilar vascular structures, was observed in the left hilar region. On the PET-CT scan, there was intense metabolic activity uptake in interactions in cells. Biopsy taken from the endobronchial lesion detected in fiberoptic bronchoscopy was reported as adenocarcinoma. The International Agency for Research on Cancer (IARC), classifies carcinogens that cause cancer development in humans into 4 groups. Welding fume exposure in our case is in group 1 accoriding to IARC.Here, we presented a occupatşonal lung cancer case related to the welding fumes.

Keywords: Welding, pneumoconiosis, malignancy

INTRODUCTION

Cancer is a multifactorial disease with complex causes of development and an increasing incidence and mortality worldwide. It is believed that this condition is caused by an increase in the prevalence of cancer-predisposing conditions with the growth of the population, aging and socioeconomic developments. Occupational exposure is thought to be responsible for 10% of lung cancer cases. This is due to the fact that in many occupational risk factors, the essential route of exposure is via inhalation. At the same time, the synergistic effect of smoking also plays a critical role in cancer development.[1-3] The International Agency for Research on Cancer (IARC), an independent scientific organization within the World Health Organization, classifies carcinogens that cause cancer development in humans into 4 groups. Factors considered to be definitely carcinogenic in humans are included in Group 1.[4] Welding fume exposure in our case is in group 1 accoriding to IARC. Here, a 51-year-old welder diagnosed as lung cancer is presented.

CASE REPORT

A 51-year-old male patient applied to our clinic with complaints of weakness and rapid fatigue that have been going on for 1 month. He has never smoked a cigarette. There was no history of cancer in his family. On physical examination, his general condition was good, vital signs were stable, respiratory sounds were heard normally during the chest examination. Laboratory values at the time of application were within normal limits. In his occupational history, it was learned that he has been working as a welder for 24 years, and exposed to mixture of welding fumes. Posteroanterior chest radiograph showed homogenous opacity in the left hilar area, 1.5 cm nodular density in the left upper zone, and a consolidated area in the left middle zone (**Figure 1**). On thoracic computed tomography, a soft tissue lesion with irregular margins, approximately 5 cm in size, surrounding the hilar vascular structures was observed in the left hilar region. In addition, a nodular lesion measuring approximately 1.7 cm with a partially irregular border was observed in the upper left lobe anterior (**Figure 2a, 2b**). On the PET-CT scan, pathological increased metabolic activity involvement was observed in the central soft tissue lesion of about 5 cm size in the left lung (SUVmax: 16.76). There was increased metabolic activity uptake in an irregularly circumscribed nodular density increase of approximately 1.7 cm in the anterior upper lobe of the left lung (SUVmax: 6.17) (**Figure 3**). No extrapulmonary involvement was observed on PET-CT. Endobronchial lesion was observed in the patient who underwent fiberoptic bronchoscopy. The biopsy taken from the lesion was reported as adenocarcinoma (**Figure 4**). Chemotherapy (Alectinib) was started by the Oncology Department for the patient who had a positive Alk mutation. The patient evaluated by the clinical council of occupational diseases was accepted as occupational lung cancer with his current occupational history, clinical and radiological findings, and his legal notification was made.

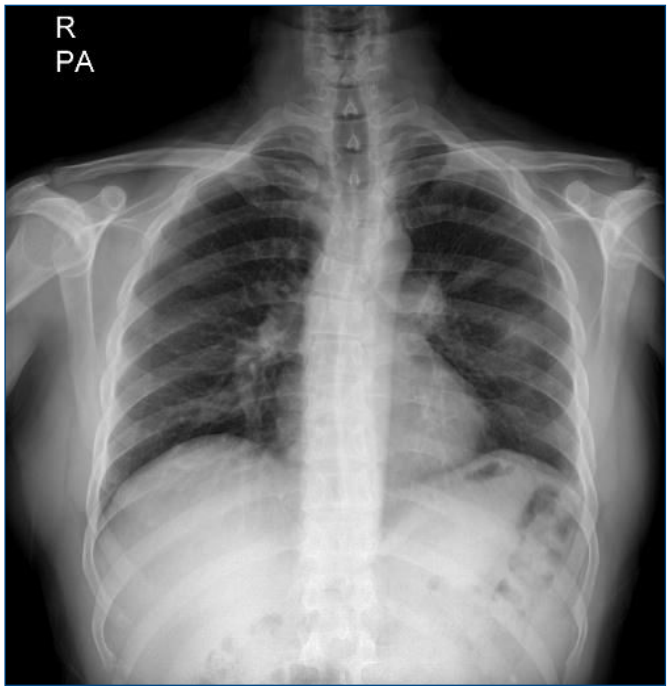


Figure-1: Chest X ray showed homogenous opacity in the left hilar area, 1.5 cm nodular density in the left upper zone, and a consolidated area in the left middle zone

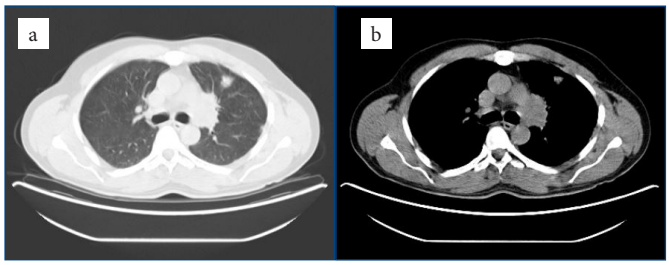


Figure-2: a, b On thoracic computed tomography, a soft tissue lesion with irregular margins, approximately 5 cm in size, surrounding the hilar vascular structures was observed in the left hilar region. In addition, a nodular lesion measuring approximately 1.7 cm with a partially irregular border was observed in the upper left lobe anterior

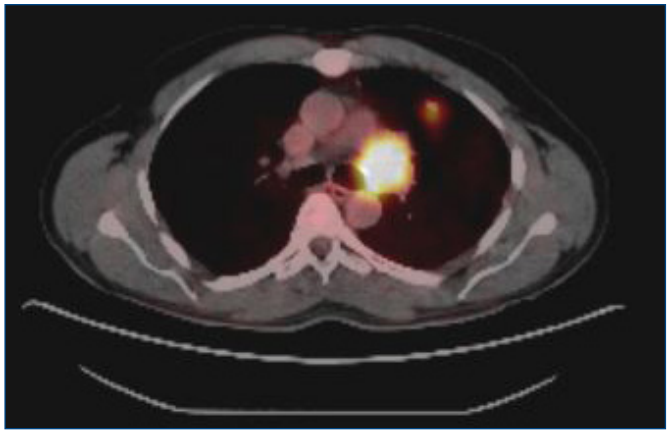


Figure-3: On the PET-CT scan, pathological increased metabolic activity involvement was observed in the central soft tissue lesion of about 5 cm size in the left lung(SUVmax: 16.76). There was increased metabolic activity uptake in an irregularly circumscribed nodular density increase of approximately 1.7 cm in the anterior upper lobe of the left lung(SUVmax: 6.17)

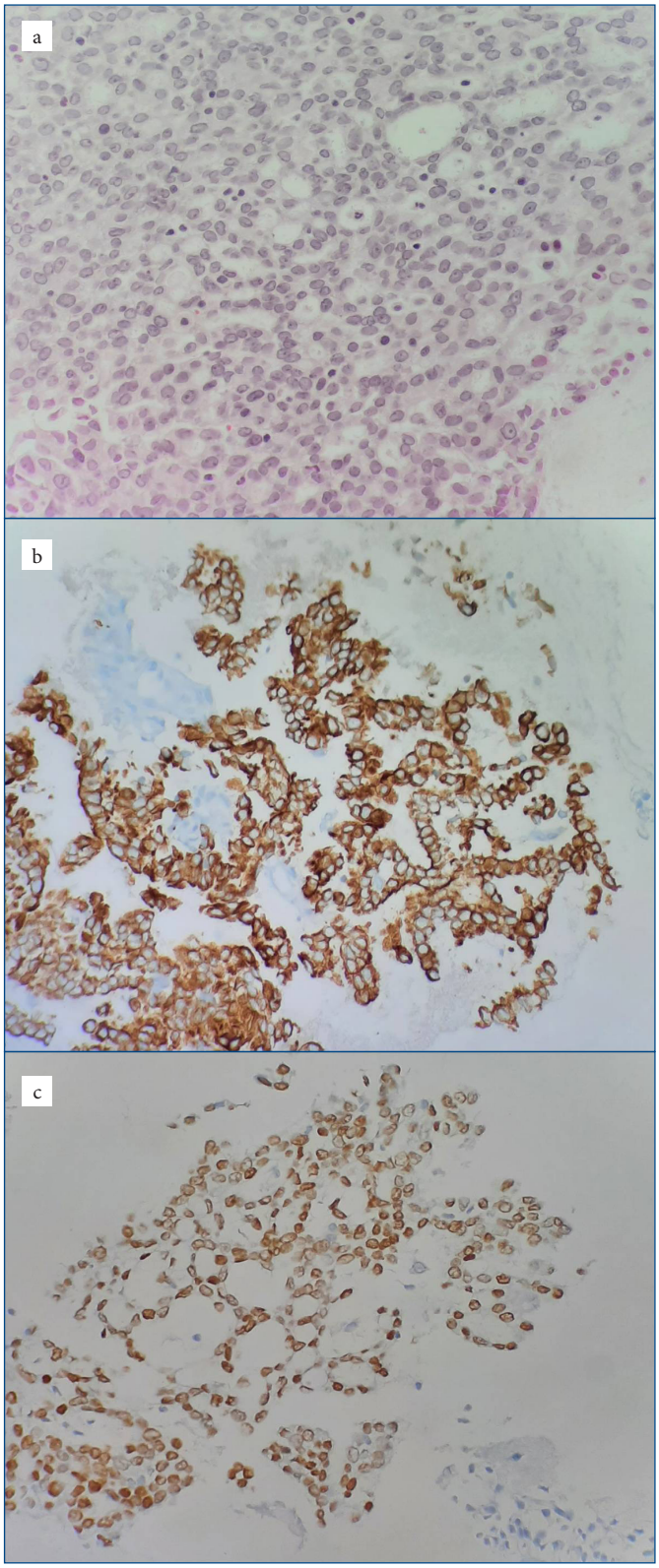


Figure-4: a Tumor cells forming a cribriform structure (HEX400)
b Keratin 7 positivity in tumor cells (Keratin 7X400)
c TTF1 positivity in tumor cells (TTF1X400)

DISCUSSION

5-10% of cancer development is explained by hereditary mechanisms, and the remaining part is attributed to the environmental and occupational factors.[5] Large cohort studies have proven the relationship between smoking and lung cancer.[6,7] The development of lung cancer in smokers is about 20%. Aproximately 90% of patients with lung cancer were also smoker.[8,9] Familial cancer syndromes are considered rare, and the majority of cancers occur sporadically.[5] Our case had never smoked and had no family history of cancer. Millions of workers in Turkey and around the world are exposed to welding fumes, which are composed of complex substances and rich in metals. Welding fumes refer to all kinds of fumes generated during the joining or cutting of metals with various welding techniques.[4] There are various welding techniques, the most common being arc welding where an arc between the filler metal and the work is the heat source (such

as Shielded metal arc welding, tungsten inert gas welding) and gas welding where energy is provided. The composition of the fumes depends on the nature of the filler metals, powders, combustibles, electrodes and electrode coatings, in addition to welding techniques.[4,10,11] The size of the weld particles formed as a result of the welding process varies between 10 nm and 20 mm depending on the process, and approximately 90% of them are smaller than 2 microns. Therefore, it can easily reached to respiratory tract.[11,12] According to the results of the IARC review, welding fumes have been identified as the definitive human carcinogen.[4] The carcinogenic feature of welding fumes have been thought as suppressing the immune system and causing chronic inflammation.[13] Solid tumors that are thought to be caused by exposure to occupational carcinogens in humans appear to develop cancer about 10-12 years or more after exposure. Cancers originating from the blood and lymphatic system, such as leukemia and lymphoma, are usually seen 3-7 years after exposure to occupational carcinogens. Hematological cancers that grow more slowly (e.g. myelodysplasia or low-grade lymphomas), on the other hand, may occur later.14 In 2006, Ambroise er al.[15] designed a meta-analysis of 66 epidemiological studies, they found that the risk of lung cancer was 26% higher in welders. Hospital-based studies in Argentina in 1999 and Finland in 2005 reported an increased risk of squamous cell carcinoma among workers exposed to welding fumes.[16,17] Paris et al.[18] reported an increased risk of adenocarcinoma among workers exposed to welding fumes in a hospital-based study in France in 2006. Our case, who had no smoking history and no family history of cancer, had a diagnosis of lung adenocarcinoma that developed 24 years after the onset of welding fumes exposure. In a case where causality and temporal relationship between cancer diagnosis and exposure were established, a legal notification was made by diagnosing occupational lung cancer.

CONCLUSION

As a result, the possibility of lung cancer should be kept in mind in the follow-up of those exposed to welding fumes, since the risk of lung cancer increases in relation to welding fumes exposure in welders.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. 1971. *Milbank Q.* 2005;83(4):731-757. doi:10.1111/j.1468-0009.2005.00398.x
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.. *CA Cancer J Clin.* 2018;68(6):394-424. doi:10.3322/caac.21492
3. Gersten O, Wilmoth JR. The cancer transition in Japan since 1951. *Demogr Res.* 2002;7:271-306. doi:10.4054/DemRes.2002.7.5
4. IARC. (2019). Agents Classified by the IARC Monographs Volumes 1–127. Accessed: 06 July 2020, http://monographs.iarc.fr/ENG/Classification/index.php
5. Fischman M. L., Rugo H. S. Occupational Cancer. LaDou J., Harri-son R. (Ed.). Current Occupational & Environmental Medicine 5th edition New York, N.Y.: McGraw-Hill Education LLC. 2014;276-307
6. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *Br Med J.* 1976;2(6051):1525-1536. doi:10.1136/bmj.2.6051.1525
7. Rogot E, Murray JL. Smoking and causes of death among U.S. veterans: 16 years of observation. *Public Health Rep.* 1980;95(3):213-222.
8. Wright GS, Gruidl ME. Early detection and prevention of lung cancer. *Curr Opin Oncol.* 2000;12(2):143-148. doi:10.1097/00001622-200003000-00008
9. Ozlü T, Bülbül Y, Oztuna F, Can G. Time course from first symptom to the treatment of lung cancer in the Eastern Black Sea Region of Turkey. *Med Princ Pract.* 2004;13(4):211-214. doi:10.1159/000078318
10. Antonini JM. Health effects of welding. *Crit Rev Toxicol.* 2003;33(1):61-103. doi:10.1080/713611032
11. Burgess, W. A. Welding. Pp. in W. A. Burgess, ed. Recognition of health hazards in industry: a review of materials and processes, 2nd ed. Wiley, New York. 1995;167-204
12. Jenkins NT, Pierce WMG, Eagar TW. Particle size distribution of gas metal and flux cored arc welding fumes. *Welding J.* 2005;84(10):156-163.
13. Guyton KZ, Rusyn I, Chiu WA, et al. Application of the key characteristics of carcinogens in cancer hazard identification. *Carcinogenesis.* 2018;39(4):614-622. doi:10.1093/carcin/bgy031
14. LaDou, J., & Harrison, R. (Eds.). Current occupational & environmental medicine. New York: McGraw-Hill. 2021;392
15. Ambroise D, Wild P, Moulin JJ. Update of a meta-analysis on lung cancer and welding. *Scand J Work Environ Health.* 2006;32(1):22-31. doi:10.5271/sjweh.973
16. Pezzotto SM, Poletto L. Occupation and histopathology of lung cancer: A case-control study in Rosario, Argentina. *Am J Ind Med.* 1999;36(4):437-443. doi:10.1002/(sici)1097-0274(199910)36:4<437::aid-ajim4>3.0.co;2-c
17. Alkjær T, Pilegaard M, Bakke M, Jensen BR. Danish National Research Centre for the Working Environment Norwegian National Institute of Occupational Health Finnish Institute of Occupational Health. *Scand J Work Environ Health.* 2005;31(2):152-159.
18. Paris C, Clement-Duchene C, Vignaud JM, et al. Relationships between lung adenocarcinoma and gender, age, smoking and occupational risk factors: A case-case study. *Lung Cancer.* 2010;68(2):146-153. doi:10.1016/j.lungcan.2009.06.007

Journal of
Pulmonology and
Intensive Care

Case Report

DOI: 10.51271/JOPIC-0011

Pulmonary hypertension rapidly leading to mortality in a patient with interstitial pneumonia with autoimmune features

Esma Zenbilli, Kerem Ensarioğlu, Tuğçe Şahin Özdemirel, Berna Akıncı Özyürek

Department of Pulmonary Medicine, Ankara Ataturk Sanatoryum Training and Research Hospital, University of Health Sciences, Ankara, Turkey

Cite this article: Zenbilli E, Ensarioğlu K, Şahin Özdemirel T, Akıncı Özyürek B. Pulmonary hypertension rapidly leading to mortality in a patient with interstitial pneumonia with autoimmune features. *J Pulmonol Intens Care.* 2023;1(2):49-51.

Corresponding Author: Kerem Ensarioğlu, kerem.ensarioglu@gmail.com

Received: 03/03/2023 ◆ **Accepted**: 09/05/2023 ◆ **Published**: 22/05/2023

Abstract

Interstitial Pneumonia with Autoimmune Features (IPAF) is a newly defined connective tissue disease (CTD) related pulmonary involvement in 2015 by the European Respiratory Society and American Thoracic Society. It is used to define the subgroup of patients with no known CTD history. In this case report, we present a patient with IPAF diagnosis, who had rapid clinical deterioration after a COVID-19 infection, which was attributed to a newly diagnosed pulmonary hypertension. A 69-year-old male patient with chronic obstructive pulmonary disease (COPD) diagnosis was on the routine follow-up for a duration of five years. He had been diagnosed with type 2 diabetes mellitus and gout, with under constant follow-up for a known cardiovascular arterial disease history. During a routine pulmonary evaluation, the patient had stated a worsening exercise capacity and an increase in coughing. The requested high-resolution computed tomography showed emphysema at the upper lobes and a reticular pattern at the lower lobes, with honeycombing, traction bronchiectasis, and ground-glass findings. After a rheumatology consultation, which excluded the presence of an underlying rheumatological disease, the patient was diagnosed with IPAF. Under immunosuppressive treatment, the patient complained of increased dyspnea at a routine follow-up after a COVID infection in 2021, and antifibrotic treatment was initiated due to the progression of pulmonary fibrosis. During routine follow-up, further limitation in exercise capacity was evident, for which extra-pulmonary involvement was investigated. Pulmonary hypertension (PH) diagnosis was confirmed with vasoreactivity positivity; however, due to both progression in IPAF and concurrent PH, the patient was lost during the follow-up. As seen in this case, despite being stable for years, the addition of another comorbidity may rapidly worsen a patient's otherwise stable clinical condition. While antifibrotic regimens may be used on a case-by-case basis, their effect on disease progression may not be sufficient to control an already present comorbidity, such as pulmonary hypertension.

Keywords: Autoimmune, mortality, interstitial pneumonia, pulmonary hypertension

INTRODUCTION

Undifferentiated connective tissue diseases (UCTD) present with varying symptoms and different system involvement. The nomenclature comes from the diagnosis itself, as no specific underlying etiology is found in patients with UCTD. A sizeable group among these patients, up to 10-25%, are diagnosed with UCTD-related interstitial lung disease (ILD) at or during the follow-up. For those whose pulmonary involvement could not be classified under any known connective tissue diseases (CTD), the European Respiratory Society (ERS) and American Thoracic Society (ATS) defined Interstitial Pneumonia with Autoimmune Features (IPAF) description in 2015 (1).

IPAF remains a rare entity among UCTD, as it is a diagnosis of exclusion and requires evaluation of possible CTD (2). The diagnostic process is further complicated as IPAF may present itself with nonspecific radiological findings such as ground-class opacities and traction bronchiectasis (2-3). Additionaly, IPAF may be insidious in clinic setting as it can mimic clinical presentation of nonspecific interstitial pneumonia and has an overall better prognosis than idiopathic pulmonary fibrosis, which often leads to an indolent process that delays the diagnosis (3-4).

In this case report, we present a patient with an IPAF diagnosis who had rapid clinical deterioration after a COVID-19 infection, which was attributed to a newly diagnosed pulmonary hypertension.

CASE

A 69-year-old male patient with chronic obstructive pulmonary disease (COPD) diagnosis was on the routine follow-up for a duration of five years. He had been diagnosed with type 2 diabetes mellitus and gout, with under constant follow-up for a known cardiovascular arterial disease history. During a routine pulmonary evaluation, the patient had stated a worsening exercise capacity and an increase in

coughing. In the physical examination, desaturation was present in room air at 80% with a finger probe and was consistent with the arterial blood gas sampling. Bilateral rales were heard in lung auscultation, with more prominent in the lower left zone. Clubbing was not evident, and there were no signs of cardiac failure.

The chest x-ray requested for initial evaluation showed a reticular pattern in the left lower zone and subpleural involvement in both lung zones. (**Figure 1**) For further investigation, high-resolution computed tomography (HRCT) was performed, which revealed emphysema at the upper lobes and a reticular pattern at the lower lobes, with honeycombing, traction bronchiectasis, and ground-glass findings present at the lower lobes. (**Figure 2**) In the connective tissue marker test panel, Scl-70 was found positive. A bronchoscopy was performed for the presence of additional pathologies, with bronchoalveolar lavage and transbronchial biopsy being non-diagnostic.

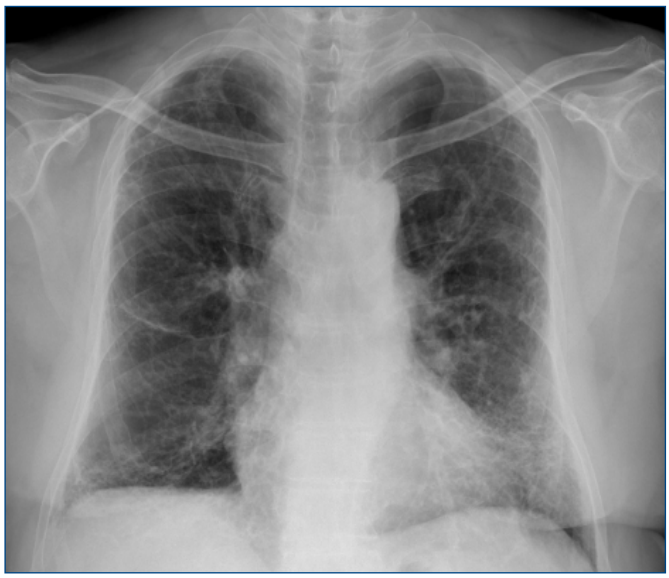


Figure 1. Chest X-ray performed at initial evaluation

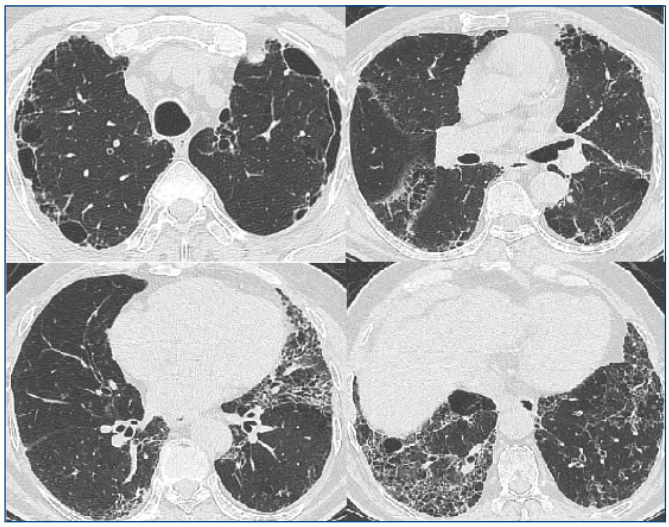


Figure 2. Tomography sections at initial evaluation

After a rheumatology consultation, which excluded the presence of an underlying rheumatological disease, the patient was diagnosed with IPAF. In a multidisciplinary council, the patient was put on an immunosuppressive regimen consisting of azathioprine and glucocorticoid. For a duration of 3 years, the patient was on the mentioned regimen, with a progressive decrease in drug dosage, and later, was on the follow-up with no treatment for two years as he was considered stable (**Figure 3**).

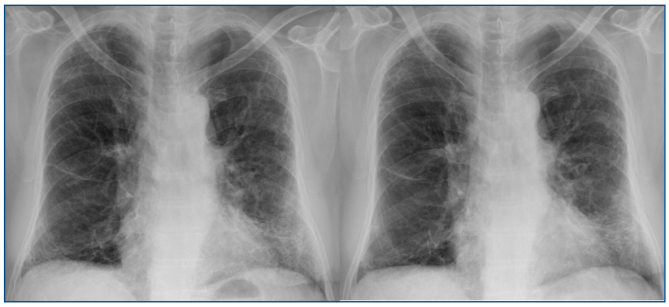


Figure 3. Chest X-ray follow-up 3 months and one year under treatment

At a routine follow-up after a COVID infection in 2021, the patient complained of an increase in dyspnea. In the requested HRCT, an increase in interstitial pattern, this time more predominant in the right lower lung, was observed (**Figure 4**). After consultation with the rheumatology department again for additional treatment requirement, the patient was evaluated once more at the multidisciplinary council, at which due to increased pulmonary fibrosis under immunosuppression, antifibrotic treatment was initiated as well nintedanib 150 mg twice daily.

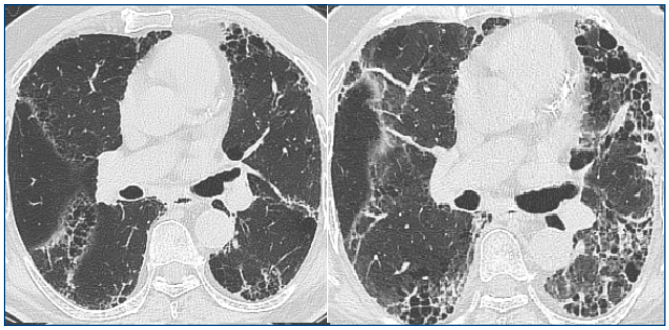


Figure 4. Tomography comparison performed at re-evaluation

During routine follow-up, further limitation in exercise capacity was evident, for which extra-pulmonary involvement was investigated. In echocardiography, an elevated systolic pulmonary arterial pressure (sPAB) of 50 mmHG was seen, and to evaluate pulmonary hypertension etiology, right heart catheterization was performed. Vasoreactivity was found positive, and the patient was put on a regimen of calcium channel blockers, for which limited response was seen. Due to respiratory failure attributed to IPAF and concurrent PHT, the patient was lost during the follow-up.

DISCUSSION

IPAF diagnosis requires four criteria; typical presentation in HRCT or a biopsy sample, exclusion of other etiologies, exclusion of known CTD and two criteria from a clinical and a serological list, which consists of CTD serological markers and clinical findings (2). Radiologically, IPAF may be presented with findings specific for non-specific interstitial pneumonia (NSIP), organizing pneumonia (OP) or combination of both, as well as lymphocytic interstitial pneumonia (LIP) (3). As NSIP is the most prevalent radiological pattern in IPAF at a 75.8%,

ground-class, reticular opacities and traction bronchiectasis are usually seen, with sparing of the subpleural areas (3). Compared to idiopathic pulmonary fibrosis (IPF), IPAF has a better prognosis, with a slow clinical deterioration (4).

IPAF treatment consists of immunosuppression as a sole agent or combined with a glucocorticoid regimen. In presence of respiratory failure, long term oxygen treatment is required for clinical control and symptomatic relief; and all patients eventually require pulmonary rehabilitation (4). Currently the justification for antifibrotic treatment is lacking due to insufficient data and studies are underway for their role in disease control (5).

Patient's Considerations

The patient, during the treatment duration, was compliant with the diagnosis and suggestions, however, expressed distress at the diagnosis of pulmonary hypertension. The informed consent for all treatment regimens and the presentation itself was received verbally and written from both the patient and the family.

CONCLUSION

As seen in this case, despite being stable for years, addition of another comorbidity may rapidly worse a patient's otherwise stable clinical condition. While antifibrotic regimens may be used as a case-by-case basis, their effect on disease progression may not be sufficient to control an already present comorbidity, such as pulmonary hypertension in this case. This limitation regarding comorbidities further stresses the point of routine evaluation and follow-up, as well as being vigilant for a possible change in treatment regimens when required.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Fischer A, Antoniou KM, Brown KK, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. *Eur Respir J*. 2015;46(4):976-987. doi:10.1183/13993003.00150-2015
2. Graney BA, Fischer A. Interstitial Pneumonia with Autoimmune Features. *Ann Am Thorac Soc*. 2019;16(5):525-533. doi:10.1513/AnnalsATS.201808-565CME.
3. Yoo H, Hino T, Han J, et al. Connective tissue disease-related interstitial lung disease (CTD-ILD) and interstitial lung abnormality (ILA): Evolving concept of CT findings, pathology and management [retracted in: Eur J Radiol Open. 2022 Feb 11;9:100402]. *Eur J Radiol Open*. 2020;8:100311. doi:10.1016/j.ejro.2020.100311
4. Fernandes L, Nasser M, Ahmad K, Cottin V. Interstitial Pneumonia With Autoimmune Features (IPAF). *Front Med (Lausanne)*. 2019;6:209. doi:10.3389/fmed.2019.00209
5. Nagy A, Nagy T, Kolonics-Farkas AM, et al. Autoimmune Progressive Fibrosing Interstitial Lung Disease: Predictors of Fast Decline. *Front Pharmacol*. 2021;12:778649. doi:10.3389/fphar.2021.778649