SARS-CoV-2-associated fatalities within the first year of the COVID-19 pandemic: an autopsy study

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Supplementary Information

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Availability of data and material
The manuscript has data included as electronic supplementary material.

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Abstract

Background: COVID-19 now exists for more than 3 years and has caused almost 7 million deaths worldwide. At the beginning of this study only little was known on the patients' characteristics and comparative autopsy studies are still rare.
Material and methods: Between 11 March 2020 and 10 March 2021, 55 consecutive and complete autopsies of individuals who died in association with SARS-CoV-2 infections were performed shortly after death (median PMI 6.8 h) by the same team. Clinical data were available in 45 of 55 cases. 1st vs. 2nd infection wave cases and male vs. female cases were compared.
Results: Thirty-five patients were male (63.6%) 20 were female (36.4%), average age 72.4 years. Seventeen cases (30.9%) could be assigned to the 1st and 38 cases (69.1%) to the 2nd infection wave. Forty-two of the decedents (76.4%) died due to COVID-19. Arterial hypertension, obesity, and cardiac hypertrophy were the most frequent detected comorbidities.
Discussion: The present study corroborates previous research data but also reveals new approaches for further comparative studies. Patient-specific personal and general ICU-related risk factors for the development of thromboembolisms oppose the effects of changes in anticoagulant medication.

Keywords
Coronavirus · Death · Autopsy · Very short postmortem interval · Severe disease progression

Introduction

The severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is an RNA virus that causes the coronavirus disease 2019 (COVID-19) [24]. Since its first description in Wuhan, China, in December 2019, it rapidly spread all over the world. On March 11 2020, the World Health Organization (WHO) "made the assessment that COVID-19 can be characterized as a pandemic" [5]. In the following months, the incidence of COVID-19 cases in Germany showed a wave-like course, similar to other viral respiratory diseases. Until today (Spring 2023) nearly 7 million people died from or in association with a SARS-CoV-2 infection worldwide, of which approximately 170,000 died in Germany [40].

Scientific literature on COVID-19 autopsies ranges from single case reports to autopsy studies with over 700 patients [10, 39]. To reduce the transmission of virus containing aerosols some research groups used postmortem imaging and minimally

Table 1 Overview of autopsy studies with full autopsies of SARS-CoV-2-associated deaths ($n \geq 10$)[a]

Autopsy study	Year	Number of full autopsies	Country	Notes
Fitzek et al. [10]	2021	283	Germany	–
Danics et al. [3]	2021	100	Hungary	–
Edler et al. [7]	2020	80	Germany	Subset of Fitzek et al.
Present study	2023	55	Germany	–
Carsana et al. [2]	2020	38	Italy	–
Kyada et al. [18]	2022	33	India	–
Puelles et al. [29]	2020	27	Germany	Subset of Fitzek et al.
Elezkurtaj et al. [8]	2021	26	Germany	–
Han et al. [14]	2020	24	USA	–
Falasca et al. [9]	2020	22	Italy	–
Schurink et al. [34]	2020	21	Netherlands	–
Jackson et al. [15]	2021	20	USA	–
Zacharias et al. [44]	2022	20	Austria	–
Menter et al. [23]	2020	17	Switzerland	–
Haberecker et al. [13]	2022	15	Switzerland	–
Swoboda et al. [36]	2021	15	Germany	Subset of the present study
Keresztesi et al. [16]	2020	15	Romania	–
Kommoss et al. [17]	2020	13	Germany	–
Wichmann et al. [41]	2020	12	Germany	Subset of Fitzek et al.
Deinhardt-Emmer et al. [4]	2020	11	Germany	Subset of the present study
Schaller et al. [30]	2020	10	Germany	–
Fox et al. [12]	2020	10	USA	–

[a]This table only includes studies in which the performed autopsies were clearly defined as full or conventional autopsies (including the examination of the brain), studies in which the number of full autopsies was not clearly visible were not considered

invasive techniques or partial/incomplete autopsies [19, 26], but many centers also conducted a number of conventional full autopsies (◻ Table 1). These examinations were usually performed within time intervals of only a few hours up to 10 days after death with an average post-mortem interval (PMI) of a few days [41, 43]. The decedents were predominantly male, elderly (average age at death approx. 50–80 years) and overweight, suffering from multiple preconditions such as cardiovascular diseases, chronic pulmonary diseases, and diabetes [13, 17]. The most reported post-mortem organ findings concerned the lungs, mainly in the form of lung fibrosis and diffuse alveolar damage (DAD), followed by affections of the kidneys and the liver that finally often led to fatal multiple organ failure [8, 22]. In addition, (micro-) thromboembolism, particularly within the pulmonary vessels, were frequently observed [7, 12, 17].

Comparative studies between study samples of different infection waves are still rare [3, 20] and often consider single organs only [11, 42]. Hence, the present retrospective study compares the autopsy findings encountered during the first and second infection wave in Germany as well as the differences between male and female patients. Thereby, the study primarily aims at the characterization of individuals, who died in association with a SARS-CoV-2 infection, including the identification of the substantial co-morbidities. Furthermore, the effects of different therapeutical measures during different times of the first year of the COVID-19 pandemic is analyzed.

Materials and methods

With approval of the local ethical board (registration number 2020-1773), 55 consecutive autopsies of individuals, who died in association with a SARS-CoV-2 infection, were performed at the Institute of Forensic Medicine of the Jena University Hospital between 11 March 2020 and 10 March 2021. Except for two, in all patients SARS-CoV-2 was detected by naso-pharyngeal swab testing prior to death. While all clinical cases were tested by PCR, this knowledge was only available to a limited extent in forensic and private cases. Based on the phase classification of the Robert Koch Institute Berlin (German public health institute for investigation and prevention of infectious diseases), two 'infection waves' (dynamics of the official nation-wide SARS-CoV-2 case detection) were defined [32]: autopsy cases from 11 March 2020 to 31 July 2020 were assigned to the 'first infection wave' and cases from 1 October 2020 to 10 March 2021 to the 'second infection wave'.

The study group finally included the following types of autopsies:
1. Clinical autopsies of deceased patients from the Jena University Hospital and 4 regional hospitals located in the German Federal State of Thuringia ($n = 45$).
2. "Private" autopsies requested by public health departments or a family member of the deceased ($n = 3$).
3. Forensic autopsies requested by departments of public prosecution of the German Federal State of Thuringia ($n = 7$).

Table 2 General characteristics of the study sample			
Characteristics	Total	First wave	Second wave
n (%)	55 (100.0%)	17 (30.9%)	38 (69.1%)
Sex, n (%)			
Male	35 (63.6%)	12 (70.6%)	23 (60.5%)
Female	20 (36.4%)	5 (29.4%)	15 (39.5%)
Age, years			
Mean	72.4	74.6	71.4
Median	77.2	80.1	72.0
Total range	19.4–96.2	52.4–91.9	19.4–96.2
Type of autopsy, n (%)			
Clinical autopsy	45 (81.8%)	17 (100.0%)	28 (73.7%)
Forensic autopsy	7 (12.7%)	0 (0.0%)	7 (18.4%)
Private autopsy	3 (5.5%)	0 (0.0%)	3 (7.9%)
Postmortem interval, hours			
Total case sample (median)	6.8	4.2	9.9
Total range	1.3–610.9	1.3–97.8	1.8–610.9
Clinical autopsies (median)	5.2	4.2	6.5
Forensic autopsies (median)	171.8	0	171.8
Private autopsies (median)	214.4	0	214.4
Place of death, n (%)			
ICU	43 (78.2%)	12 (70.6%)	31 (81.6%)
Normal ward	7 (12.7%)	5 (29.4%)	2 (5.3%)
Home	5 (9.1%)	0 (0.0%)	5 (13.2%)
n number of cases, *%* Percent, *ICU* intensive care unit			

All cases were autopsied as soon as possible after death in order to achieve a very short post-mortem interval (PMI; time between death and autopsy), facilitating optimal morphological post-mortem diagnostics due to minimal tissue degradation, even in tissues that usually loose histomorphological quality very fast (e.g. gastrointestinal samples). A short PMI was essentially achieved by close and reliable cooperation between all players involved (ICUs, forensic department, and the patient's relatives). Clinical autopsies were conducted with consent of the relatives only. All autopsies were complete autopsies, i.e. post-mortem examination of all internal organs and tissues of all body cavities, and performed by the same team. The leg vessels were autopsied only if thromboembolisms had previously been found in other organs or vessels. The main objectives of the autopsies were the determination of the cause of death, the recording of findings possibly typical (or even specific) for COVID-19, and the detection of the morphological comorbidities.

During each autopsy, a total of at least 60 tissue and organ samples were collected for comprehensive histological and immunohistochemical analyses.

After autopsy, a categorization of SARS-CoV-2 positive deaths was done according to a modification of the proposal by Edler et al. (2020) [4]:

– Category 1: Death is due to COVID-19 alone.
– Category 2: Death is due to COVID-19 and due to at least one another severe disease.
– Category 3: Death is not due to the detected SARS-CoV-2 infection.
– Category 4: Cause of death is undetermined.

In addition, medical records, including clinical data and metadata on the deceased patients, were respectively provided by the participating clinical institutions and the customers of the autopsies. These data included information on diagnosis and treatment, police investigation results, and death certificates. Medical records were completely available in 45 of the 55 cases. In forensic and private autopsy cases, the collection of such information

was not possible or only possible to a limited extent.

Statistical analyses were performed with MS Excel 16 (Version 2301, 2023), IBM SPSS Statistics 27 (2020), IDL 8.8.0 (2020), and GraphPad Prism 4.00 (2003). P-values were calculated using the Fisher-Yates test and student's t-test. P-values < 0.05 were considered statistically significant.

Results

Total study sample

The general characteristics of the study sample are shown in ◘ Table 2. Out of the 55 SARS-CoV-2-associated death cases autopsied 35 cases (63.6%) were male, and 20 cases (36.4%) were female, predominantly in older age (median 77.2 years). The PMI was very low (median 6.8 h), and even lower when considering the clinical autopsy cases only (81.8% of the cases, median 5.2 h). Most patients (43 cases, 78.2%) died on an Intensive Care Unit (ICU).

The medical diagnoses determined at autopsy are summarized in Table S1. The vast majority of the present patient sample (37 cases, 67.3%) died directly from a COVID-19 pneumonia, accordingly, classified as category 1 (38 cases, 69.1%). One fatality of category 1 was due to pulmonary embolism alone. Four patients (7.3%) died from a combination of COVID-19 with another severe disease (e.g. intracerebral hemorrhage) and were classified as category 2. In 10 cases (18.2%), death could not unambiguously determined due to the proven SARS-CoV-2 infection (category 3) because death was caused by another severe and concomitantly existing condition, such as drowning, or ileus due to a malignant tumor disease.

Except for three cases, all patients suffered from at least one substantial comorbidity. The three most frequent substantial comorbidities were 'arterial hypertension' (52.7%), 'obesity' (47.3%), and 'cardiac hypertrophy' (40.0%). Accordingly, the 'circulatory system' as well as the 'endocrine and metabolic system' were found to be the most frequent disease groups. The group of 'malignant neoplasms' was the third frequent group. In 10 of the 18 autopsy cases (55.6%) with a malignant tumor disease,
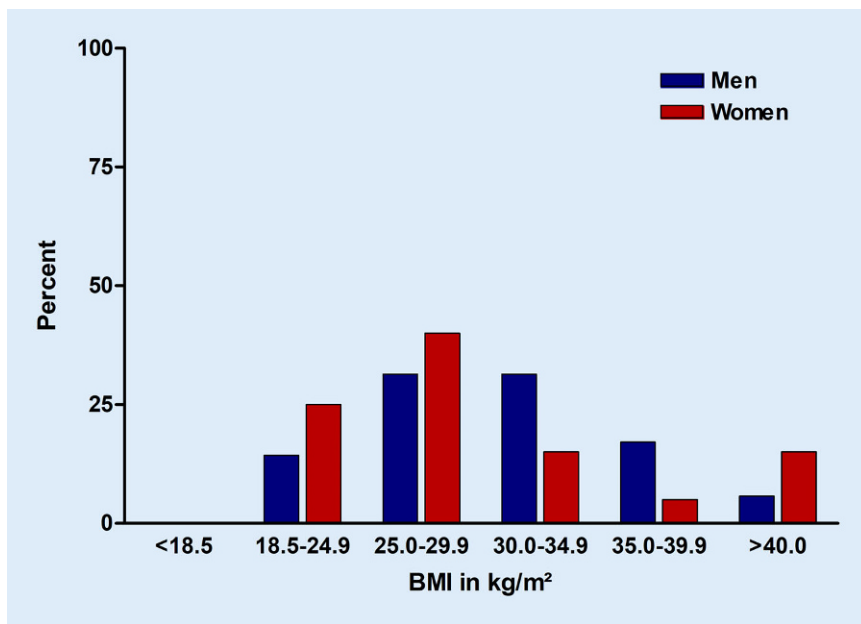
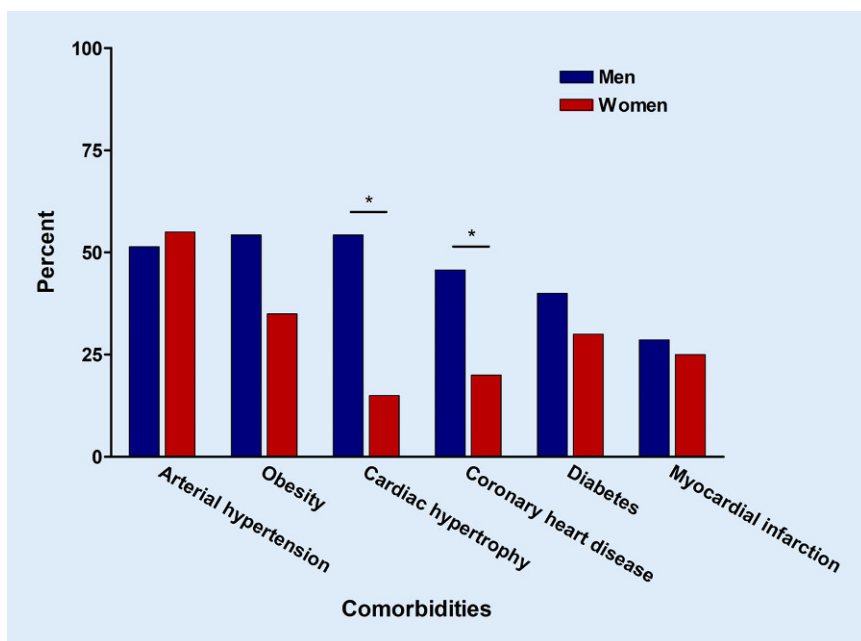**Fig. 1** ▲ Comparison between the BMI in males and females

Fig. 2 ▲ Substantial comorbidities in males and females. *Statistically significant ($p < 0.05$)

the neoplasm was first diagnosed at autopsy. These tumors were chronic lymphocytic leukemia, endometrium carcinoma, prostate carcinomata, colorectal carcinomata, pancreatic precancer, hepatocellular carcinoma and liposarcoma. With exception for the endometrium carcinoma case, which showed evidence for lymphangiosis, no other tumor case revealed any sign of metastatic spread. In one case, the can-

cer diagnosis was made only a few days prior to death (cervical carcinoma).

Thromboembolic findings could be observed in 61.8% of the cases. None of the patients showed sole thromboses. Either there were no thromboembolic findings at all or a combination of thrombi and emboli.

The majority of our study group (45 cases, 81.8%) was overweight with

a median body mass index (BMI) of $29.4\,\text{kg/m}^2$.

Comparison between 1st and 2nd infection wave

A data comparison between 1st and 2nd infection wave is shown in ▣ Tables 2, S1 and S2. Seventeen cases (30.9%) could be assigned to the 1st infection wave, and 38 cases (69.1%) to the 2nd infection wave.

Concerning sex, age, place of death, and BMI, no significant differences were found between 1st and 2nd wave. In terms of the substantial comorbidities, endocrine diseases significantly predominated in the 1st wave ($p = 0.007$) and cardiovascular diseases in the 2nd wave ($p = 0.043$).

The relative case number of intubated patients in the second wave almost doubled from 41.2% ($n = 7$) in 1st wave to 78.6% ($n = 22$) in 2nd wave ($p = 0.011$). Considering anticoagulant and antiviral medication, the changes from Enoxaparin ($p = 0.002$) and Lopinavir/Ritonavir (Kaletra®) ($p = 0.001$) in the 1st wave to Tinzaparin ($p < 0.001$) and Remdesivir ($p = 0.001$) in the 2nd wave were striking. In addition, the number of patients treated with immunosuppressants (mainly dexamethasone) and multiple antibiotics increased significantly ($p = 0.031$).

Comparison between male and female patients

A data comparison between male and female patients is shown in Tables S3 and S4 and ▣ Figs. 1, 2 and 3. Even though the mean BMI was not significantly different, women tended to be overweight (mean BMI $29.5\,\text{kg/m}^2$), while men were mostly obese (mean BMI $31.0\,\text{kg/m}^2$) (▣ Fig. 1). The most frequent place of death was the ICU in both groups; however, women died significantly more often on a normal ward ($p = 0.045$). The mean durance of hospitalization in general (19.7 days vs. 11.9 days; $p = 0.043$) and the length of stay in the intensive care unit (15.5 days vs. 10.8 days; $p = 0.042$) in particular was significantly longer in male patients.

While the majority (regardless of sex) died due to COVID-19 (74.3% of the men and 60.0% of the women), in female decedents the cause of death was not
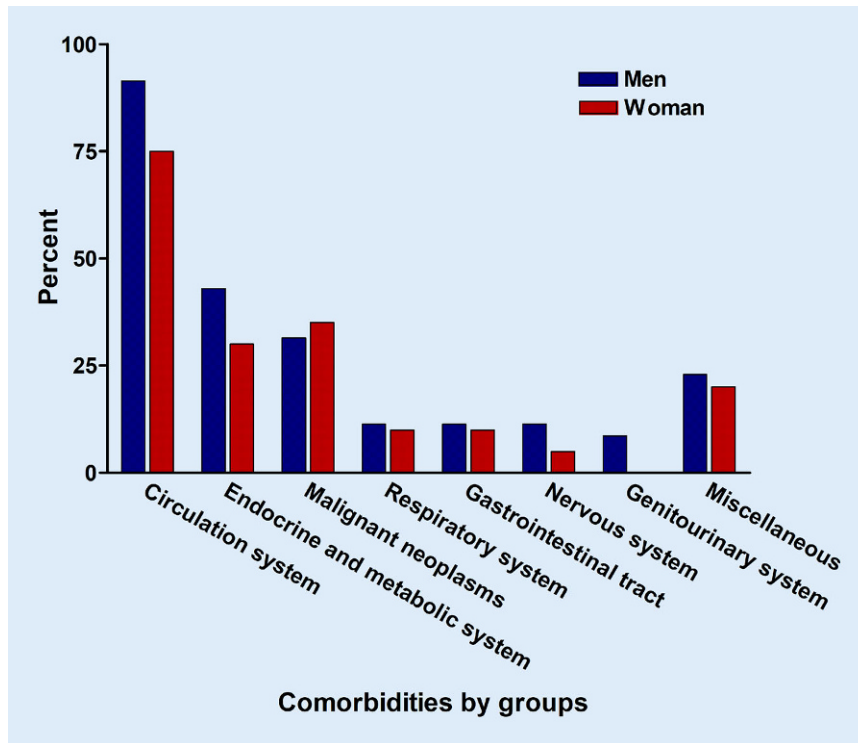
Fig. 3 ▲ Comparison of comorbidities by groups in males and females

associated with COVID-19 more frequent ($p = 0.017$).

The most frequent comorbidities in both sexes were arterial hypertension and obesity. Men suffered from cardiac hypertrophy ($p = 0.004$) and coronary heart disease ($p = 0.039$) more often compared to women (◨ **Fig. 2**). Sorted by groups, diseases of the circulatory system are the most common comorbidities in both sexes, followed by diseases of the endocrine and metabolic system and malignant neoplasms in male patients (◨ **Fig. 3**).

60.0% of women ($n = 12$) but only 25.7% of men ($n = 9$) showed no thromboembolic findings at all. If thromboembolisms were found, pulmonary embolisms were observed significantly more often in male decedents ($p = 0.028$).

No woman but 7 men (24.1%) were intubated and artificially ventilated with ECLS ($p = 0.034$). In addition, the proportion of female patients with no artificial ventilation was significantly higher ($p = 0.005$) and men had been artificially ventilated significantly longer ($p = 0.042$).

Concerning medication, both groups were treated approximately equally with one exception: administration of antiviral drugs was more infrequent in females ($p = 0.031$), especially Lopinavir/Ritonavir (Kaletra®) ($p = 0.031$), which was only used in males.

Discussion

The present study focused on the determination of characteristics of 55 SARS-CoV-2-associated autopsy cases and the analysis of the effects of therapeutical measures during the first year of the COVID-19 pandemic. We were able to ensure the best possible autopsy findings by means of a median post-mortem interval (PMI) of 6.8 h, which is, to the best of our knowledge, the lowest in European and American literature on COVID-19 autopsies.

The average age of the deceased of the present study (72.4 years) corresponds to the results of other studies [1, 3]. However, this average age differs from the average age at death of other large German studies, such as in the Hamburg study by Edler et al. [7] (mean 79.2 years). This discrepancy may be due to the different study design. While "the health authorities of the districts [of the City of Hamburg] ordered autopsies for all COVID-19 deaths according to the Infection Protection Act" [35], the case

sample of the present study mainly consists of clinical patients with a severe clinical course of COVID-19.

The most frequent substantial comorbidities of the present COVID-19 study sample, i.e. cardiovascular diseases, obesity and diabetes, match those of other autopsy studies (◨ **Table 1**) and are common preconditions in Germany. However, it is striking that the proportion of patients suffering from arterial hypertension and from an obesity is higher in our study group than in the average German population [25, 31]. Additionally considering other publications [37], this confirms that these illnesses must highly likely be considered risk factors for a severe course of COVID-19.

Another remarkable result concerning the comorbidities of the present COVID-19 decedents is that 10 of 18 malignant neoplasms found during autopsy were unknown ante-mortem. This finding supports the hypothesis that even unknown malignancies could have considerable influence on the course of COVID-19. Since previous autopsy studies on COVID-19 only appraise active, diagnosed tumor diseases [30, 34], further investigation on this point appears to be promising.

In line with many other COVID-19 autopsy studies [8, 10, 18], the present COVID-19 study sample revealed thromboembolic findings in many different organs, primarily affecting pulmonary arteries. However, as described by Dwiputra Hernugrahanto et al. [6], even more unusual locations such as cerebral or splenic vessels could be detected as well. Despite significant changes in anticoagulant therapy, observed by comparing the 1st and 2nd infection wave, and contrary to our expectations, we observed an increase in thromboembolic findings. In 2015, a meta-analysis of Malato et al. [21] found that deep vein thrombosis (DVT) occurred in approximately 1 of 8 ICU patients. Even with exclusion of clinical studies evaluating the presence of DVTs in patients without antithrombotic medication, this percentage only slightly decreased. Furthermore, while Pereyra et al. [27] were able to show that the administration of low-molecular-weight heparin in COVID-19 patients "was associated with reduced mortality"; other non-COVID-19-

related publications did not reveal any difference between the use of Tinzaparin and Enoxaparin [28, 38]. To summarize, the afore-mentioned considerations suggest that the effect of anticoagulation in critically ill patients like in the present study sample may be negated by general and ICU specific risk factors, regardless of the antithrombotic drugs (Tinzaparin or Enoxaparin) administered.

The non-significantly increased high number of thromboembolic findings in the 2nd infection wave might also be the reason why the number of our patients dying directly from COVID-19 did not decrease either. Based on the present statistics, one patient (5.9%) of the 1st wave died from a COVID-19 induced pulmonary embolism, whereas 5 patients (13.2%) of the 2nd wave showed fatal thromboembolic findings of the lungs on top of a COVID-19 pneumonia.

Inherently, the present study has some limitations. First, the case number is rather small but still one of the more extensive compared to other full autopsy studies (see ◘ Table 1). Second, our study population underlies a selection bias as it is mainly composed of clinical patients with severe courses of COVID-19. However, using this deliberately chosen study design (i.e., examining those who were apparently most affected), we hoped for obtaining a deeper understanding on the new virus disease as quick as possible. Third, control cases are missing. While the investigation of this particular study sample enabled us to record rarer complications of the disease, it also means that our results cannot be easily extrapolated to the general (German) population where mild disease courses were predominant [33].

Conclusions

– The present study group mainly consist of elderly, obese, mostly male COVID-19 patients; nearly all of the 55 patients suffered from more than one severe comorbidity.
– COVID-19 was the cause of death in over 75% of the patients.
– Despite changes in medication and clinical treatment, no significant differences in terms of age, BMI, thromboembolic findings, and days in

clinic respectively days on ICU were detected between decedents of the 1st and 2nd infection wave.
– Thromboembolic events could be found in more than half of the cases (61.8%) with pulmonary embolism affecting men more frequently than women.

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Declarations

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Zusammenfassung

SARS-CoV-2-assoziierte Todesfälle innerhalb des ersten Jahres der COVID-19-Pandemie: eine Autopsiestudie

Hintergrund: Seit mehr als 3 Jahren verursachte COVID-19 bislang weltweit fast 7 Mio. Todesfälle. Zu Beginn dieser Studie war vergleichsweise wenig über die Charakteristika dieser Patienten bekannt und vergleichende Obduktionsstudien existieren bislang kaum.

Material und Methoden: Zwischen dem 11. März 2020 und dem 10. März 2021 wurden 55 Personen, die im Zusammenhang mit SARS-CoV-2-Infektionen verstarben, von dem selben Team vollständig obduziert. Die Obduktionen wurden kurz nach dem Tod durchgeführt (medianer PMI 6,8 h). In 45 von 55 Fällen waren zudem klinische Daten verfügbar. Verglichen wurden Fälle der ersten und zweiten Infektionswelle sowie männliche und weibliche Patienten.

Ergebnisse: 35 Patienten waren männlich (63,6 %) und 20 weiblich (36,4 %); das Durchschnittsalter betrug 72,4 Jahre. 17 Fälle (30,9 %) konnten der ersten und 38 Fälle (69,1 %) der zweiten Infektionswelle zugeordnet werden. 42 Verstorbene (76,4 %) starben direkt an COVID-19. Arterielle Hypertonie, Adipositas und Herzhypertrophie waren die am häufigsten nachgewiesenen Vorerkrankungen.

Diskussion: In Bezug auf die Hauptcharakteristika der COVID-19-Todesfälle bestätigen die Ergebnisse der vorliegenden Studie im Wesentlichen bisherige Forschungsdaten, zeigten aber auch neue Ansätze für weitere Vergleichsstudien auf. Patientenspezifische persönliche und allgemeine intensivmedizinische Risikofaktoren für die Entwicklung von Thrombembolien stehen den Auswirkungen einer Änderung der gerinnungshemmenden Medikation entgegen.

Schlüsselwörter

Coronavirus · Tod · Obduktion · Sehr niedriges postmortales Intervall · Schwere Krankheitsverläufe