Critical Care

BRIEF REPORT

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Intracranial hemorrhage in COVID-19 patients during extracorporeal membrane oxygenation for acute respiratory failure: a nationwide register study report

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Abstract

Background: In severe cases, SARS-CoV-2 infection leads to acute respiratory distress syndrome (ARDS), often treated by extracorporeal membrane oxygenation (ECMO). During ECMO therapy, anticoagulation is crucial to prevent device-associated thrombosis and device failure, however, it is associated with bleeding complications. In COVID-19, additional pathologies, such as endotheliitis, may further increase the risk of bleeding complications. To assess the frequency of bleeding events, we analyzed data from the German COVID-19 autopsy registry (DeRegCOVID).

Methods: The electronic registry uses a web-based electronic case report form. In November 2021, the registry included $N = 1129$ confirmed COVID-19 autopsy cases, with data on 63 ECMO autopsy cases and 1066 non-ECMO autopsy cases, contributed from 29 German sites.

Findings: The registry data showed that ECMO was used in younger male patients and bleeding events occurred much more frequently in ECMO cases compared to non-ECMO cases (56% and 9%, respectively). Similarly, intracranial bleeding (ICB) was documented in 21% of ECMO cases and 3% of non-ECMO cases and was classified as the immediate or underlying cause of death in 78% of ECMO cases and 37% of non-ECMO cases. In ECMO cases, the three most common immediate causes of death were multi-organ failure, ARDS and ICB, and in non-ECMO cases ARDS, multi-organ failure and pulmonary bacterial ± fungal superinfection, ordered by descending frequency.

Interpretation: Our study suggests the potential value of autopsies and a joint interdisciplinary multicenter (national) approach in addressing fatal complications in COVID-19.

Keywords: Autopsy, Registry, COVID-19, ECMO, Intracranial bleeding, Bleeding events

Introduction

Venovenous extracorporeal membrane oxygenation (VV-ECMO) is used for refractory severe acute respiratory failure with a survival rate of about 50% [1]. The interface between blood and non-biological ECMO circuit elements requires therapeutic anticoagulation, predisposing patients to an increased risk of bleeding.

Based on a recent analysis from the Extracorporeal Life Support Organization (ELSO) registry including

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7579 patients from 2007 to 2018, 37% experienced any bleeding event, and 21.2% experienced bleeding combined with a thrombotic event. While the most common bleeding events with cannulation (15.5%) and surgical site (9.6%) bleeding are easy to handle, intracranial hemorrhage occurred in only 4.5% and has been consistently associated with poor survival [2]. Other retrospective studies reported intracranial hemorrhage in 6–35.4% of patients during ECMO therapy [3–5].

Causes of intracranial hemorrhage in ECMO patients may be associated with heparin overdose, circuit-associated defibrination, thrombocytopenia, disseminated intravascular coagulation, acquired von Willebrand syndrome, and also COVID-19-associated endotheliitis. Importantly, intracranial hemorrhage was observed in many patients receiving VV-ECMO without coagulopathy or anticoagulant use [6].

In this respect, we analyzed preliminary data from the German COVID-19 Autopsy Registry [7], involving 63 deceased COVID-19 patients who received ECMO for acute respiratory failure. Specifically, we address the following questions, comparing COVID-19 autopsy cases that received ECMO support with cases that did not:

1. What differences in demographical characteristics exist?
2. What are the prevalences of bleeding events, specifically intracranial bleeding events found at autopsy?

Patient inclusion, data acquisition and management, and cohort stratification were performed as previously described [8] and are provided in the Additional file 1.

For analyses, $N=1129$ autopsy cases with positive COVID-19 test (preclinical, clinical, or post-mortem, point of care antigen test from nasopharyngeal or pulmonary swabs or PCR test from nasopharyngeal or pulmonary swabs or tissue samples) were eligible in the German COVID-19 Autopsy Registry (DeRegCOVID). 20–22% of the COVID-19 autopsy cases were located in the East and West, respectively and 28–30% in the North and South of Germany, respectively by patient residential region (Fig. 1a) or by the autopsy center region (Fig. 1b), respectively.

The percentage of COVID-19 ECMO autopsy cases of all autopsied cases increased with each pandemic wave, from 2% in the first pandemic wave to 6% in the second and 12% in the third wave (Fig. 1c).

$N=63$ patients underwent ECMO therapy. The male to female ratio in this cohort was 5:1 with a homogeneous distribution of females over the different age range of < 30–80 years, and a male peak in the age range of 51–70 years (Fig. 1d). Of the remaining $N=1065$ COVID-19 non-ECMO autopsy cases (one value missing), the male to female ratio was 2:1, with male peaks at 61–90 years and female predominance at > 90 years of age (Fig. 1e). The percentage of COVID-19 ECMO autopsy cases in the respective sex/age group was higher for males compared to females, however, in the younger age groups, total numbers were relatively low, resulting in large effects of single cases on the percentage (Fig. 1f).

Any kind of a bleeding event was found in 56% of ECMO cases ($N=35$ cases) and 9% of non-ECMO cases ($N=100$ cases, p value < 0.0001). Intracranial bleeding (ICB) was documented in $N=13$ ECMO cases (21%) and in $N=30$ non-ECMO cases (3%, p value < 0.0001, Fig. 1g). In ECMO patients with ICB, in three cases ($N=2$ soft tissue bleeding due to cannulation and $N=1$ epistaxis) and in non-ECMO patients with ICB, in three cases extracranial bleeding events were documented, respectively ($N=2$ acute posthemorrhagic anemia not otherwise specified and $N=1$ recurrent bleeding of the lower gastrointestinal tract, a detailed specification of bleeding events is provided in Fig. 1h). In 78% of ECMO cases and 37% of non-ECMO cases with ICB, the intracranial bleeding was classified as the immediate or underlying cause of death. The five most common immediate causes of death were multi-organ failure, DAD/ARDS, ICB, pulmonary bacterial ± fungal superinfection and extracranial bleeding events in $N=63$ ECMO cases and DAD/ARDS, multi-organ failure, pulmonary bacterial ± fungal

(See figure on next page.)

Fig. 1 **a** Number of COVID-19 autopsy cases and percentage of COVID-19 autopsies after ECMO therapy by postal code of the deceased person (1 value missing of ECMO cases, 17 values missing of non-ECMO cases). **b** Number of COVID-19 autopsy cases and percentage of COVID-19 autopsies after ECMO therapy by postal code of the contributing center. **c** Individual disease duration (orange bars) or death date (black boxes, when no data on symptom onset/ first positive SARS-CoV-2 test was available) in $N=63$ ECMO COVID-19 autopsy cases. **d** Age and sex distribution in COVID-19 autopsies after ECMO therapy ($N=63$). **e** Age and sex distribution in COVID-19 autopsies without ECMO therapy ($N=1065$, 1 value missing). **f** Age and sex distribution in COVID-19 autopsies as a percentage of respective age group. **g** Intracranial bleeding (ICB) and other hemorrhages in ECMO and non-ECMO COVID-19 cases. The associations between the variables ECMO and ICB and ECMO and any bleeding event were significant (both p value < 0.0001 Fisher's exact test, two-tailed). Note that the number of bleeding events exceeds the number of patients, because in N = 3 non-ECMO, and $N=3$ ECMO autopsies, both ICB and other bleeding events were present at the autopsy, respectively. **h** ECMO cases (violet) and non-ECMO cases (dark yellow) with any bleeding event. The number of extracranial bleeding events is higher compared to **h**, because, in $N=4$ ECMO cases, two different extracranial bleeding events were documented. ICB, intracranial bleeding

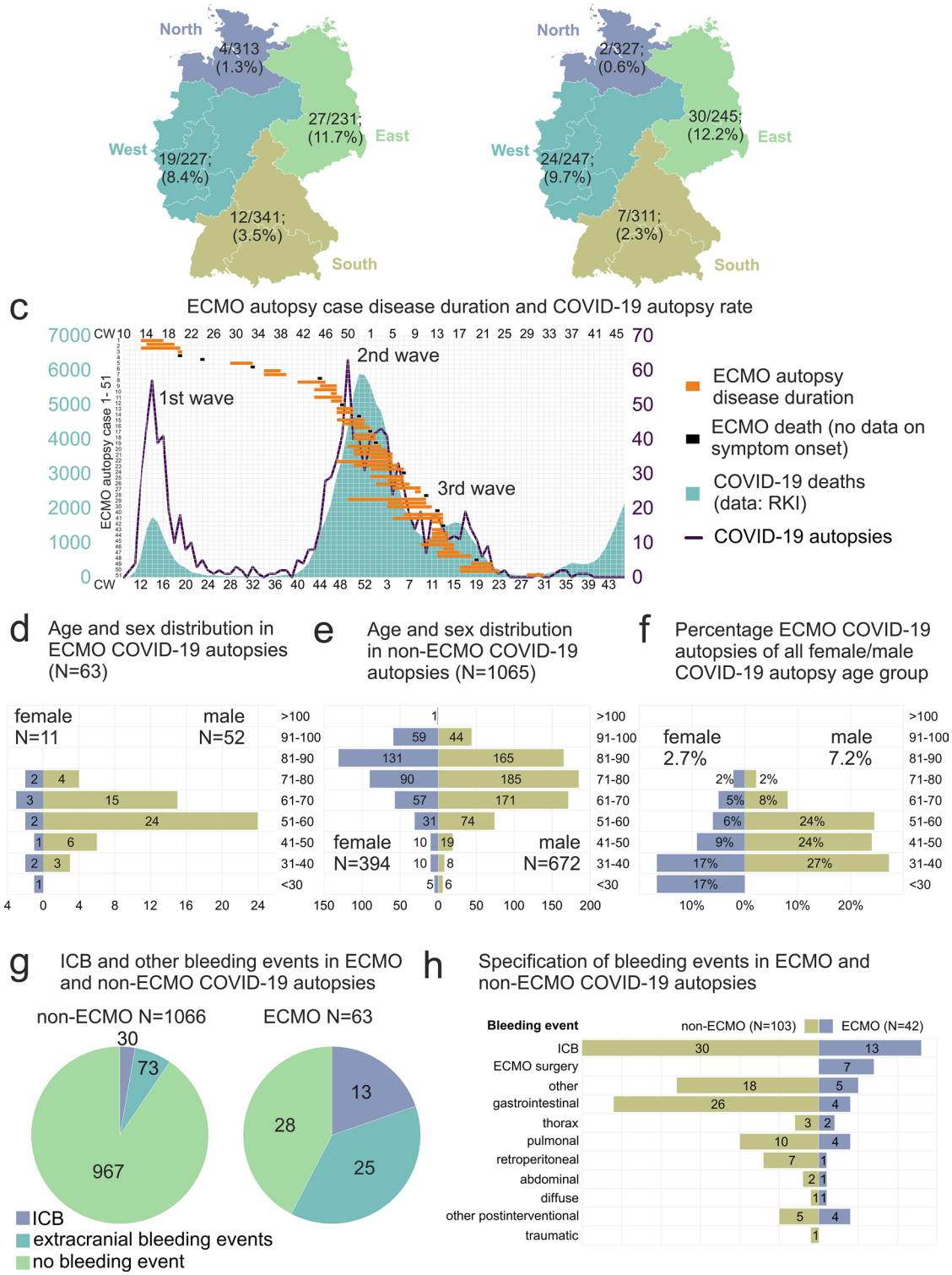

Fig. 1 (See legend on previous page.)

superinfection, pulmonary embolism, and ischemic heart disease in $N=1031$ non-ECMO cases with the complete cause of death data (ordered by descending frequency).

VV-ECMO used in refractory severe acute respiratory failure is associated with an increased risk of bleeding, of which intracranial hemorrhage has been consistently associated with very poor survival. In this report, we analyzed data from the German Registry of COVID-19 Autopsies (DeRegCOVID) to gain further insights into COVID-19 ECMO autopsy cases with bleeding events in comparison to non-ECMO cases.

ECMO being more often documented in younger and male patients, is in line with data from the Extracorporeal Life Support Organization (ELSO) Registry [3].

The prevalence of any bleeding event in more than 50% of COVID-19 ECMO autopsy cases is higher compared to a previous multicenter observational study of 152 consecutive non-autopsy patients with severe COVID-19 supported by ECMO in four UK commissioned centers during the first wave of the COVID-19 pandemic (30.9% major bleedings) [9]. This might be explained by our cohort consisting of fatal cases, which may lead to an overrepresentation of cases with bleeding events. Also, all macroscopically identified bleeding events are documented, irrespective of major bleeding criteria [10], as these data are usually not available at autopsy. Our findings regarding the prevalence of intracranial bleeding and associated mortality are consistent with a report from three tertiary care ECMO centers in Germany and Switzerland [11]. In an observational study from Northern Germany, the observation of intracranial bleeding in COVID-19 non-autopsy ECMO patients (35.4%) was higher compared to our findings. In a study from a single tertiary center on 25 non-COVID ECMO autopsy cases, 52% had intracranial macrohemorrhages [12]. However, it is possible, that due to concerns regarding occupational hazards, the omission of brain examination especially during the first pandemic wave led to an underreporting of intracranial hemorrhage at autopsy in our cohort.

Limitations

The registry only gathers data available to pathologists at the time of autopsy. The clinical information provided during autopsies is usually comprehensive, particularly regarding treatment approaches such as ECMO. Still, we cannot exclude missing data in the registry on potential ECMO therapy. Another limitation is the missing specific data on invasive ventilation therapy and missing reliable data on the mode and time of anticoagulant therapy in our cohort. Because we aimed at the broadest possible participation in the registry, the eCRF does not cover therapy and intensive care details and duration of ventilation or ECMO therapy. Considering that in more than 50% of our cohort, the immediate cause of death at autopsy was COVID-19 DAD/ARDS, it is likely that some of these patients underwent invasive ventilation therapy before death in hospitalized cases [8].

In conclusion, our report showed autopsy-confirmed increased prevalence of bleeding events and intracranial hemorrhages as causes of death in COVID-19 patients with ECMO treatment, compared to those without ECMO treatment. This illustrates the value of autopsies and a joint interdisciplinary multicenter (national) approach in addressing fatal complications in intensive care.

Abbreviations

ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; DAD: Diffuse alveolar damage; DeRegCOVID: German COVID-19 Autopsy Registry; eCRF: Electronic case report form; ELSO: Extracorporeal Life Support Organization; ICB: Intracranial bleeding; PCR: Polymerase chain reaction; RWTH Aachen University: Rhenish-Westphalian Technical University Aachen; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; VV-ECMO: Venovenous extracorporeal membrane oxygenation.

Supplementary Information

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Additional file 1. Supplementary Methods and Discussion.

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Authors' contributions

Drs SVS and PB had full access to all of the data in the study and take responsibility for the integrity of the data, which were provided by the study collaborators, and the accuracy of the data analysis. Concept and design: SVS, RDB, RR, PB. Acquisition, analysis, or interpretation of data: SVS, RDB, RR, PB. Drafting of the manuscript: SVS, RDB, RR, PB. Obtained funding: Boor. Administrative, technical, or material support: SVS, RDB, RR, PB. Supervision: PB. All authors and collaborators approved the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Only cases with a consent given by the deceased or next of kin for autopsy or request for autopsy by the health authorities or by the prosecutor's office were included in the registry. The registry was approved by the ethical committee of the medical faculty of the RWTH Aachen University (EK 092/20). Additionally, each participating center had a local ethical approval. The registry was registered with the German Clinical Trials Registry [13].

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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