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ORIGINAL

Extracorporeal membrane oxygenation: evolving epidemiology and mortality

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Abstract

Purpose: The evolution of the epidemiology and mortality of extracorporeal membrane oxygenation (ECMO) remains unclear. The present study investigates the evolving epidemiology and mortality of various ECMO techniques in Germany over time, used for both severe respiratory and cardiac failure.

Methods: Data on all patients receiving venovenous (vv-ECMO) and venoarterial (va-ECMO) ECMO as well as pumpless extracorporeal lung assist/interventional lung assist (PECLA/ILA) outside the operating room in Germany from 1 January 2007 through 31 December 2014 were obtained from the Federal Statistical Office of Germany and analyzed.

Results: The incidence of vv-ECMO and va-ECMO in the population increased threefold from 1.0:100,000 inhabitants/year in 2007 to a maximum of 3.0:100,000 in 2012, and from 0.1:100,000 in 2007 to 0.7:100,000 in 2012 and to a maximum of 3.5:100,000 in 2014, respectively. The incidence of arteriovenous PECLA/ILA also increased from 0.4:100,000 to a maximum of 0.6:100,000 in 2011, but decreased thereafter to 0.3:100,000 in 2014. The relative proportion of older patients receiving ECMO is steadily increasing. In-hospital mortality decreased over time and reached 58 and 66 % for vv-ECMO and va-ECMO in 2014, respectively. In addition, mortality steadily increased with age and was especially high in the first 48 h of ECMO use.

Conclusions: In a high-income country like Germany, the use of ECMO has been rapidly increasing since 2007 for both respiratory and cardiac support, with a recent plateau in vv-ECMO use. In-hospital mortality decreased with increasing ECMO utilization, but remains high, especially in older patients and in the first 48 h of use.

Keywords: Extracorporeal membrane oxygenation, Extracorporeal carbon dioxide removal, Epidemiology, Indication, Technical development

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Take-home message: The current study shows, for the first time, recent epidemiological data of ECMO utilization and associated mortality in a high-income country. This real-world data suggests that, although mortality decreased with increasing experience, it remained high in both venovenous and venoarterial ECMO.

Introduction

The technical aspects of modern extracorporeal membrane oxygenation (ECMO) are rapidly improving, allowing for the treatment of patients with the most severe forms of respiratory or cardiac failure [1–3]. Different forms of access to the patients' vessels are technically feasible: venovenous (vv), venoarterial (va), or arteriovenous (av) circuits. The last of these, a pumpless circuit using the native arterial pressure to generate flow, primarily allows for extracorporeal CO_2 removal ($ECCO_2R$), with limited ability to provide oxygenation [1, 4]. While vv-ECMO provides only respiratory support, va-ECMO may provide both respiratory and cardiac support. Importantly, the various techniques differ considerably, not only in regard to their indications, but also in their technical requirements, contraindications, complications, duration of application, and costs. We will use the term ECMO to refer to this set of extracorporeal techniques.

A landmark 2009 randomized controlled trial suggested that the use of vv-ECMO in cases of severe respiratory failure may improve outcomes [5]. This trial generated considerable interest in the use of ECMO in this patient population. Likewise, the 2009 influenza A(H1N1) pandemic spurred an increase in ECMO utilization [6–9]. The use of vv-$ECCO_2R$ and av-$ECCO_2R$ to enhance lung-protective ventilation in patients with less severe forms of acute respiratory distress syndrome (ARDS) is beginning to increase. Similarly, their use in patients with primary hypercapnic respiratory failure, most importantly chronic obstructive pulmonary disease (COPD), also appears to be on the rise [10–13]. Overall, the reported mortality for ECMO in severe lung failure ranges from 25 % in selected patient groups [7] to more than 60 % in larger epidemiological studies [14].

In much the same way, va-ECMO for cardiac support is growing [15]. This may be due, in part, to recent scientific evidence suggesting that cardiac support provided by intra-aortic balloon pumping (IABP) is of questionable benefit in patients with heart failure following acute myocardial infarction [16, 17], thus emphasizing the need to look for other therapeutic options in this setting. Recent data for va-ECMO in cardiac failure have shown promising results in young patients with fulminant myocarditis [18] or acute myocardial infarction [19]. With this in mind, an increasing role for va-ECMO in cardiac failure has been suggested [20, 21]. Furthermore, in propensity matched analyses comparing mortality for in-hospital resuscitation to conventional CPR, va-ECMO (extracorporeal CPR) appears promising [2, 22, 23], further emphasizing the potential role of va-ECMO in these settings. Nevertheless, reported mortality remains high within a wide range of 43–93 % [2].

Importantly, however, it remains unclear how recent scientific findings are translated into real-life medicine. Therefore, the present study was undertaken to demonstrate the epidemiologic development of ECMO utilization and associated mortality with three different techniques, namely vv-ECMO, av-$ECCO_2R$, and va-ECMO, in recent years in a high-income country such as Germany.

Patients and methods

Data were obtained from the Federal Statistical Office of Germany (Statistisches Bundesamt, Wiesbaden, Germany). According to the German accounting method for the German Health Care System, all ECMO procedures are reported to the Federal Statistical Office of Germany, as required by law. This is based on OPS codes (Operationen-und Prozedurenschlüssel). OPS is the German modification of the International Classification of Procedures in Medicine and serves as the official classification of operational procedures. The authors received official permission from the Federal Statistical Office of Germany (Statistisches Bundesamt, Wiesbaden, Germany) to publish the current data. The Institutional Review Board of University Witten-Herdecke approved the analyses contained herein without the need to obtain ethical approval.

Evaluating OPS codes from the Federal Statistical Office of Germany allowed the consideration of the country as a whole and therefore reliable epidemiologic data assessment. On 31 December 2014, the total population of Germany was 81,197,500 people as indicated by the Federal Statistical Office of Germany with minor changes during the last 10 years. However, for annual incidence calculations the total population of the corresponding year was used.

No data for co-morbidities and outcome of the patients are provided by OPS codes, since, in general, only data related to the procedures (OPS) or diagnosis (International Statistical Classification of Diseases and Related Health Problems-ICD) are transmitted from hospitals and insurance companies to the Federal Statistical Office of Germany without additional information about the individual patient. Furthermore, the ICD codes are not specific for certain entities. Therefore, the real incidence of specific disease states or syndromes, such as the acute respiratory distress syndrome (ARDS) or cardiogenic shock, cannot be estimated from this data. ARDS for example can be encoded by ARDS (J80), sepsis (A41, R57, etc.), duration of mechanical ventilation (A06-18), trauma (A06-18), or respiratory insufficiency (J96). Therefore, it was not feasible to report the 'true' incidence of ARDS or cardiogenic shock in Germany based on the ICD and OPS data.

Up until 2005, pumpless extracorporeal lung assist (PECLA), interventional lung assist (ILA), and va-ECMO were not specifically encoded. The terms PECLA and ILA are used synonymously in this paper. In 2006, a specific code for PECLA/ILA (8-852.2×) was introduced. In 2007, va-ECMO in the ICU (8-852.3×) was likewise encoded. Vv-ECMO is encoded independently of the blood flow (8-852.0×), including low-flow vv-$ECCO_2R$ systems for hypercapnic respiratory failure and high-flow vv-ECMO for severe hypoxemic respiratory failure. Therefore, epidemiologic data from 2007 through 2014 were considered. ECMO procedures, which are done only in the operating theater or catheter laboratory for cardiothoracic or thoracic surgery are encoded differently and were excluded from this analysis, as their use in this setting reflects separate—albeit potentially related—trends in the use of extracorporeal techniques. All patients who were transferred with ECMO from the operating theater to the ICU are included in the study.

Results

Epidemiology and associated mortality of ECMO in Germany

The incidence of vv-ECMO for respiratory failure increased from 1:100,000 in 2007 to 3:100,000 in 2012 and decreased to 2.4:100,000 in 2014. A maximum of 2468 patients received vv-ECMO in 2012, with a decrease to 1944 cases in 2014. In 2014, 20 % of the patients were younger than 40 years of age, 33 % of the patients were between 40 and 60, and fully 47 % were above 60 years of age (Fig. 1a). The evolution of in-hospital mortality of patients receiving vv-ECMO is illustrated in Fig. 1b. Here, the in-hospital mortality slightly decreased over time with the highest in-hospital mortality of 70.0 % in 2008 and a nadir of 56.6 % reached in 2013 while levelling out at 58.1 % in 2014.

The incidence of PECLA/ILA was lower with 0.4:100,000 in 2007 (287 cases), increasing to 0.6:100,000 in 2011 (521 cases), followed by a decrease to 0.3:100,000 in 2014 (248 cases) (Fig. 2a). In-hospital mortality of patients receiving PECLA/ILA decreased from a maximum of 65.5 % in 2008 to 49.6 % in 2014 (Fig. 2b).

The incidence of va-ECMO (Fig. 3a) increased substantially from 96 cases in 2007 (incidence 0.1:100,000) to 575 cases in 2012 (incidence 0.7:100,000) to 2268 cases in 2013 reflecting an incidence of 2.8:100,000. This number further increased in 2014 to a maximum of 3.5:100,000 (2873 cases). A corresponding decrease in the number of patients receiving IABP is seen since 2012 (supplemental Fig. 1). In 2014, 14 % of patients with va-ECMO were younger than 40 years of age, 34 % of the patients were

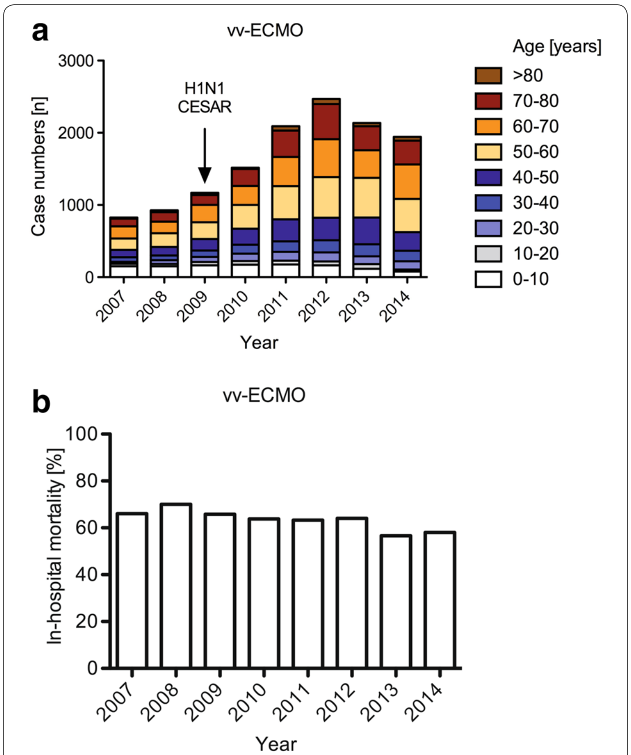

Fig. 1 Case numbers and associated in-hospital mortality of patients receiving vv-ECMO for severe respiratory failure from 1 January 2007 to 31 December 2014. The CESAR trial is discussed in Ref. [5]

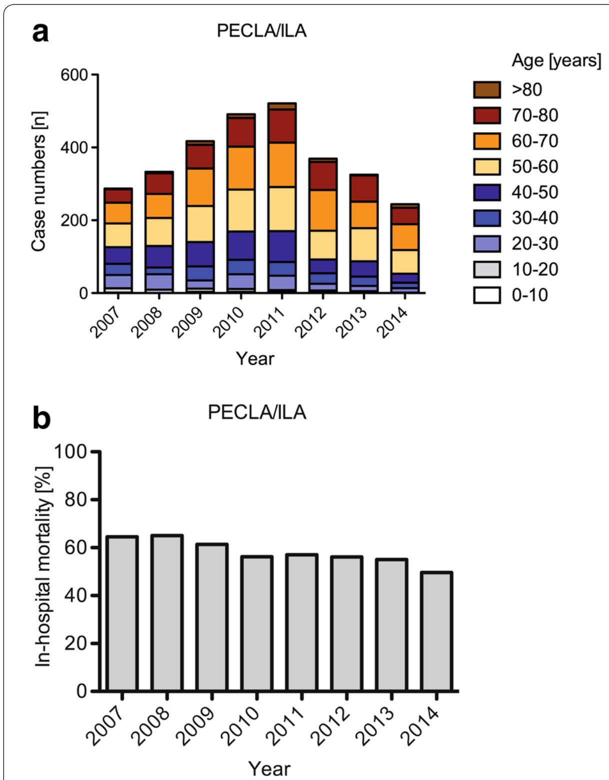

Fig. 2 Case numbers and associated in-hospital mortality of patients receiving PECLA/ILA (av-$ECCO_2R$) for severe respiratory failure from 1 January 2007 to 31 December 2014

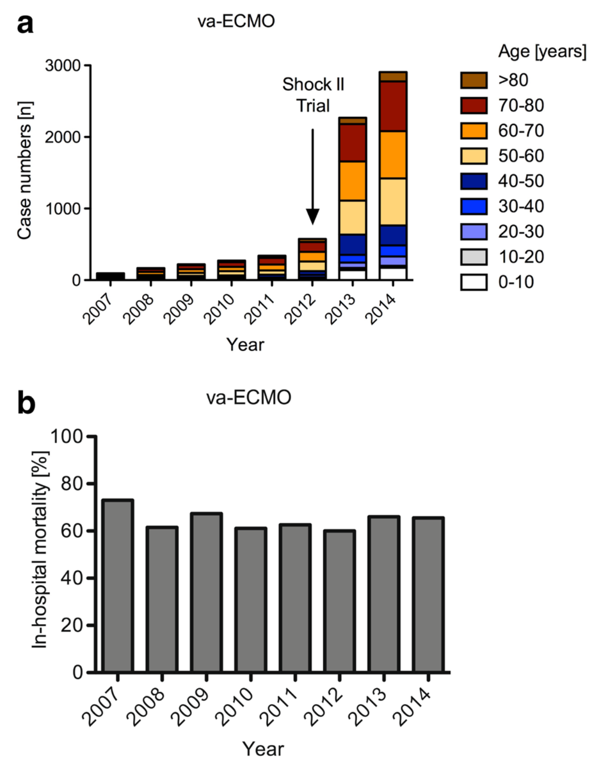

Fig. 3 Case numbers and associated in-hospital mortality of patients receiving va-ECMO for severe heart failure from 1 January 2007 to 31 December 2014. The Shock II trial is discussed in Refs. [16, 17]

between 40 and 60, and 52 % of the patients were older than 60 years of age. The evolution of in-hospital mortality of patients receiving va-ECMO is illustrated in Fig. 3b. Here, the in-hospital mortality tended to decrease over time: 73.0 % in 2007 and 65.5 % in 2014, respectively, although it remains high.

The duration of ECMO application considerably varied among individual patients ranging from less than 2 days to more than 24 days. This is illustrated in Fig. 4, displaying 2014 as a representative year. In this year, nearly a quarter of all vv-ECMO patients received ECMO for less than 2 days (Fig. 4a), and more than one-third of all va-ECMO patients for less than 2 days (Fig. 4b). Of note, in-hospital mortality was highest during both short-term and long-term ECMO application, and this was true for both vv-ECMO (Fig. 4c) and va-ECMO (Fig. 4d). The lowest mortality was observed for patients receiving vv-ECMO for 6–12 days (minimum 42.8 % for 8–10 days). Mortality steadily increased with increasing patient age, with older vv-ECMO (Fig. 5a) and va-ECMO (Fig. 5b) patients, respectively, being more likely to die. Highest mortality was noted in patients over 80 years of age, with a 76 % mortality in vv-ECMO and 77 % in va-ECMO. Remarkably, in 2014, one vv-ECMO patient and six va-ECMO patients were older than 90 years of age, respectively; the vv-ECMO patient and two out of the six va-ECMO patients survived.

Technical developments in ECMO

The use of a new double-lumen cannula, which was specifically encoded, continued to increase from 117 cases in 2013 to 150 cases in 2014.

Discussion

This is the first detailed epidemiologic study on ECMO utilization and associated mortality in a high-income country, in this case Germany. The main findings of the present analysis are as follows: First, ECMO utilization for the management of severe respiratory failure steadily and substantially increased from 2007 (particularly from 2009) until 2012, when a plateau of ECMO use was reached with a small decrease in the application of ECMO through the end of 2014. Second, ECMO utilization for cardiac support dramatically increased in 2013 with its peak in 2014; correspondingly, IABP utilization substantially decreased in 2013 and 2014. Third, in line with the increasing ECMO utilization, in-hospital mortality decreased over time, but remains high at 58 % for vv-ECMO and 66 % for va-ECMO in 2014, respectively. Fourth, the duration of ECMO application broadly varied with both short-term and long-term application being observed. Of note, very short ECMO application of less than 48 h was a frequent finding, which was true for both respiratory and cardiac support. Importantly, in-hospital mortality was highest for short-duration ECMO use. Fifth, all age groups received ECMO, with middle-aged and older patients more frequently receiving ECMO compared to younger patients, particularly with increasing ECMO experience over the years. Again, this was true for both respiratory and cardiac support, and older patients were more likely to die; although, in one sense, ECMO was shown to be feasible in very old patients.

Even though in-hospital mortality decreased over time the present study clearly shows that the mortality remains high. Interestingly, the in-hospital mortality for vv-ECMO in Germany was almost identical compared to recent data from the USA [14]. These real-life data conflict with the experience of specialized ECMO centers worldwide, reporting lower mortality rates [6, 7, 9, 24–28]. Reporting bias may account for some of this difference and a lack of standardization of indications may create confounding by indication. In addition it is likely that some centers treating only few patients per year are less experienced as there are no networks in Germany restricting ECMO treatment to specialized reference centers. Consequently, this would clearly contribute to the observation of higher real-life mortality rates in

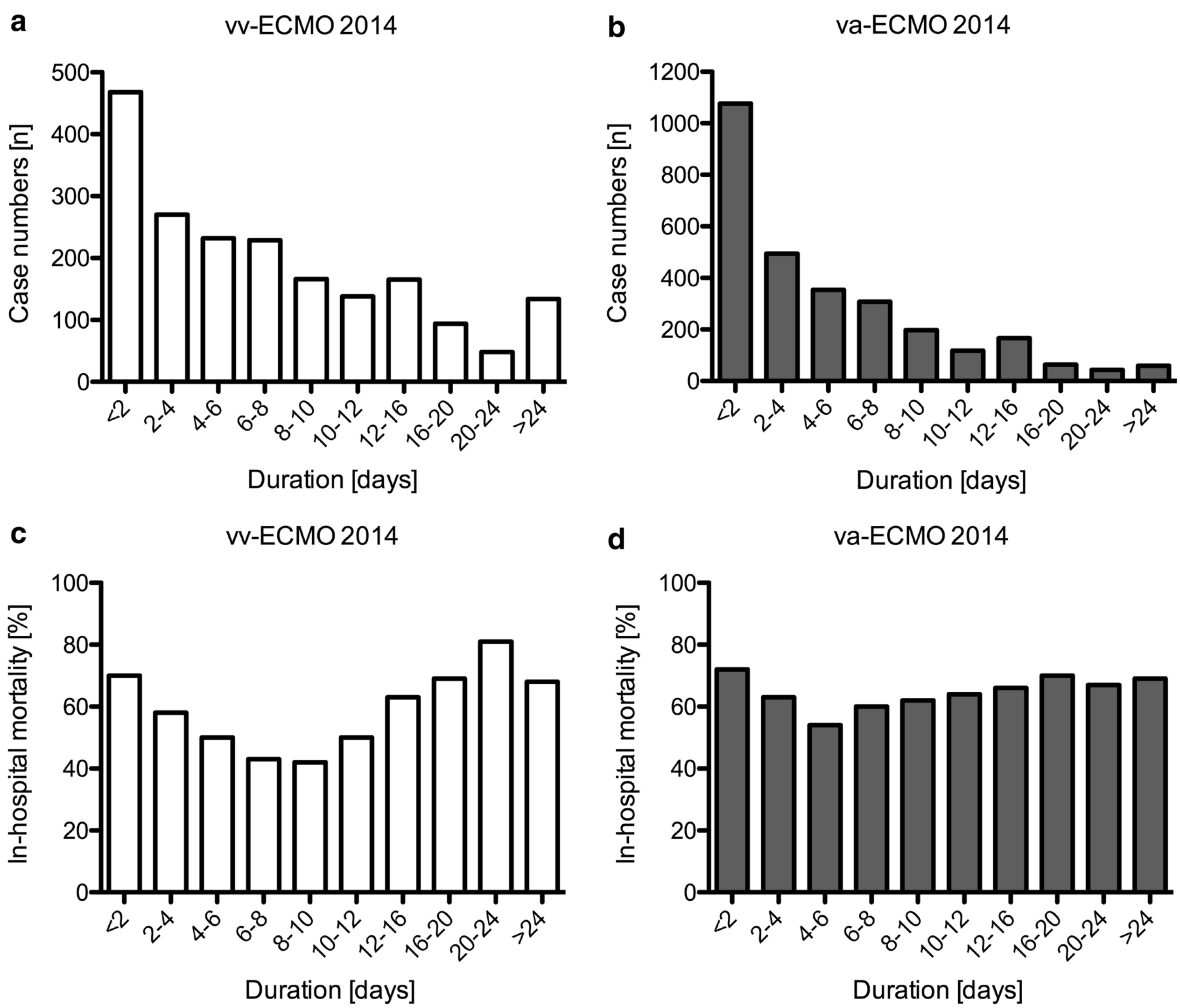

Fig. 4 Case numbers and associated in-hospital mortality of patients receiving vv- and va-ECMO in 2014 in respect of the duration of assistance. Of note, there is no subclassification in the German DRG system for durations of more than 24 days

ECMO patients as shown previously [29]. Nevertheless, further efforts should be aimed at reducing the still high in-hospital mortality.

Importantly, a quarter of all patients in 2014 received vv-ECMO for less than 48 h, and only 30 % of these patients survived. As recovery from severe respiratory failure usually takes longer, the need for ECMO in some patients was perhaps questionable to start with. The current analysis found that 70 % of patients with short-term vv-ECMO use died. This is not in accordance with the CESAR trial, which showed a prolonged survival of patients receiving ECMO for several days with a low mortality in the first days [5]. Again, this suggests the need to apply ECMO in specialized reference centers. There is also a need for clear inclusion criteria for ECMO treatment, which should be a target for further investigation. Likewise, risk prediction should also be further investigated, in order to allow us to better predict mortality in all age groups.

The in-hospital mortality rate steadily increased with advancing age, and that was again true for both respiratory and cardiac support. Nevertheless, we would not categorically exclude older patients from ECMO application, but rather suggest that more studies are needed to define selection criteria and suitability based on age. This also has been outlined previously [28, 30].

In regard to the mortality data, one of the main questions that remains is how ECMO use has increased to

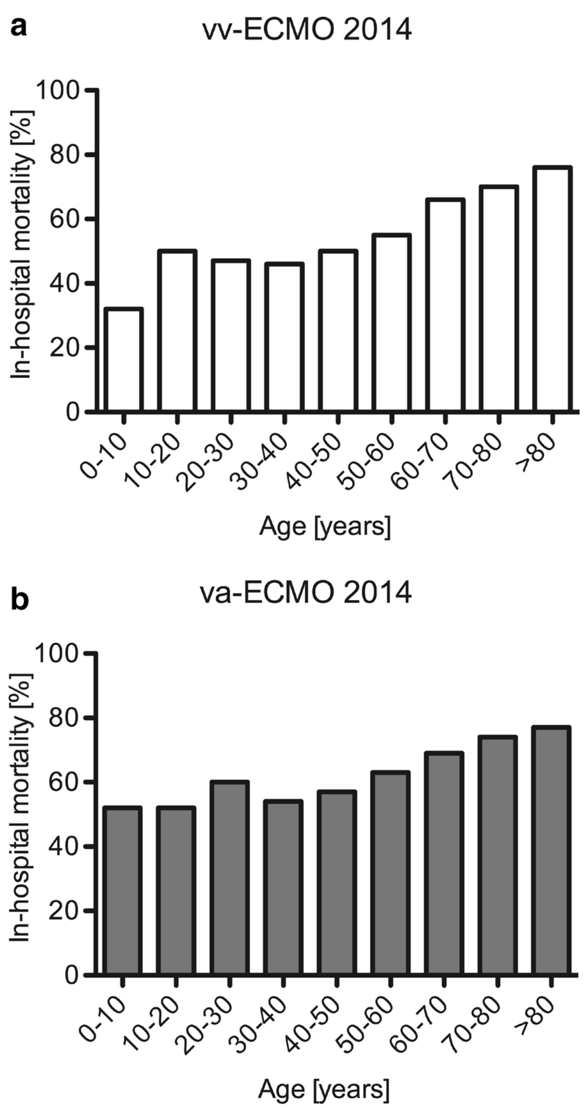

Fig. 5 In-hospital mortality of patients receiving vv- and va-ECMO in respect of the age exemplarily shown for 2014

such a high incidence? It is of note that the influenza A(H1N1) pandemic in 2009, the results of important landmark trials published in 2009 concerning H1N1 patients and non-H1N1 patients [5, 7], and technical improvements of ECMO available in 2010, respectively, occurred more or less simultaneously. This was followed by a steep increase in ECMO utilization between 2009 and 2012. However, other secular trends in the general management of these patients—including mechanical ventilation, sedation practices, and transfusion practices—could also have affected the outcomes in ECMO patients. Therefore, the precise impact of landmark trials and technical developments on ECMO evolution remains unclear.

Another important issue is that the applications of different modern ECMO systems seem to be interdependent. Two observations support this: First, there was a clear reduction in the use of pumpless av-$ECCO_2R$ since 2011. Presumably, this is attributable to technical simplifications of vv-ECMO appearing in Germany in 2010. vv-ECMO is associated with fewer complications, particularly related to the fact that arterial cannulation is not required, and additionally may allow for better oxygenation. This is advantageous when hypoxemic and hypercapnic respiratory failure occur simultaneously. Second, the negative results of the IABP Shock II trial [16, 17] were almost certainly the reason for the marked reduction of IABP utilization. This trend was accompanied by a corresponding increase in va-ECMO use to support cardiac function. However, the connection between these two findings requires further investigation.

Our study has several limitations. It is unclear if the current findings of ECMO utilization in Germany are transferrable to other high-income countries. For example, in France the incidence of vv-ECMO for ARDS patients was estimated to be 1 case per 100,000 inhabitants [31], which is lower than in Germany. However, there are two potential confounders: First, Germany provides a high number of ICU beds in relation to the number of inhabitants [32, 33]. Second, in Germany there are no governmental restrictions for the utilization of ECMO or PECLA/ILA in hospitals, and the reimbursement for the application of all of these systems is individually negotiated between hospitals and insurance companies. Frequently, this is in contrast to other countries. In addition, no data for incidence of ARDS or cardiogenic shock are available in Germany, since encoding for these certain entities is not specific enough in the German DRG system. Moreover, the present study could not provide data for center size and center numbers. Future real-life studies should, however, link outcomes with center experience and size as was recently done using a large registry of ECMO cases worldwide [29]. Moreover, the current outcome data were not able to distinguish between children and adults. This, however, needs further investigation. Finally, health-related quality of life, long-term survival, and health care costs could not be estimated from the current data as noted above. This should be a target of future studies.

In conclusion, there is a recent increase in ECMO utilization in Germany, which is associated with a reduction in the in-hospital mortality. Importantly, the overall mortality in German ECMO patients, particularly in patients with short-term ECMO use and older patients, still remains high, which is in contrast to findings of prospective studies performed by highly experienced research groups. This suggests the need for specialized reference ECMO centers in order to concentrate experience and optimize patient outcomes. In addition, the current findings underline the importance of conducting further well-designed clinical studies and to provide technical refinements in order to continue to improve ICU outcomes in patients receiving extracorporeal cardiac or pulmonary support.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4273-z) contains supplementary material, which is available to authorized users.

Abbreviations

$ECCO_2R$: Extracorporeal CO_2 removal; ECMO: Extracorporeal membrane oxygenation; vv-ECMO: Venovenous extracorporeal membrane oxygenation; va-ECMO: Venoarterial extracorporeal membrane oxygenation; IABP: Intra-aortic balloon pumping; PECLA/ILA: Pumpless extracorporeal lung assist/interventional lung assist.

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Compliance with ethical standards

Conflicts of interest

C.K. received travel grants, lecture fees and performs consultant services for Maquet, Rastatt, Germany; D.B. is on the Medical Advisory Boards for ALung Technologies and Kadence. All compensation for these activities goes to Columbia University. S.S. received travel grants and lecture fees from Maquet Cardiopulmonary, Rastatt, Germany, E.S. has no conflicts of interest, A.P. received travel grants from Maquet Cardiopulmonary, Rastatt, Germany, T.B. received honoraria for lectures and activities as member of the advisory board of Novalung, Heilbronn, Germany, T.M. received travel support for invited lectures from Maquet Cardiopulmonary, Rastatt, Germany; W.W. received fees for advisory board meetings and lectures from Maquet Cardiopulmonary, Rastatt, Germany. C.K. and W.W. received an open research grant for the hospital from Maquet Cardiopulmonary, Rastatt, Germany.

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