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Journal of Cardiac Failure Vol. 00 No. 00 2022

Extracorporeal Membrane Oxygenation for Graft Dysfunction Early After Heart Transplantation: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a prevailing option for the management of severe early graft dysfunction. This systematic review and individual patient data (IPD) meta-analysis aims to evaluate (1) mortality, (2) rates of major complications, (3) prognostic factors, and (4) the effect of different VA-ECMO strategies on outcomes in adult heart transplant (HT) recipients supported with VA-ECMO.

Methods and Results: We conducted a systematic search and included studies of adults (≥18 years) who received VA-ECMO during their index hospitalization after HT and reported on mortality at any timepoint. We pooled data using random effects models. To identify prognostic factors, we analysed IPD using mixed effects logistic regression. We assessed the certainty in the evidence using the GRADE framework. We included 49 observational studies of 1477 patients who received VA-ECMO after HT, of which 15 studies provided IPD for 448 patients. There were no differences in mortality estimates between IPD and non-IPD studies. The short-term (30-day/in-hospital) mortality estimate was 33% (moderate certainty, 95% confidence interval [CI] 28%−39%) and 1-year mortality estimate 50% (moderate certainty, 95% CI 43%−57%). Recipient age (odds ratio 1.02, 95% CI 1.01−1.04) and prior sternotomy (OR 1.57, 95% CI 0.99−2.49) are associated with increased short-term mortality. There is low certainty evidence that early intraoperative cannulation and peripheral cannulation reduce the risk of short-term death.

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Manuscript received June 30, 2022; revised manuscript received August 27, 2022; revised manuscript accepted November 1, 2022.

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Funding: The authors report no funding sources.

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1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2022.11.011

Conclusions: One-third of patients who receive VA-ECMO for early graft dysfunction do not survive 30 days or to hospital discharge, and one-half do not survive to 1 year after HT. Improving outcomes will require ongoing research focused on optimizing VA-ECMO strategies and care in the first year after HT. (*J Cardiac Fail 2022;00:1–14*)
Key Words: ECMO, heart transplantation, graft dysfunction, prognosis, meta-analysis.

Introduction

Early graft dysfunction (EGD) is a common cause of mortality after heart transplantation (HT), accounting for nearly two-thirds of deaths in the first 30 days after HT.[1] Graft dysfunction early after HT is classified as primary graft dysfunction (PGD), which accounts for the majority of cases, or secondary to a specific etiology such as sepsis, hyperacute rejection, or surgical complications.[1] Severe EGD often requires short-term mechanical circulatory support (MCS), and its success depends on the timing of the initiation of support, preexisting patient comorbidities, and the severity of peripheral organ hypoperfusion.[2]

In recent years, venoarterial extracorporeal membrane oxygenation (VA-ECMO) has become one of the most widely used forms of short-term MCS.[3] Severe EGD may be a life-threatening but reversible process, and VA-ECMO can be used as a bridge to recovery or, less commonly, re-HT. Our current understanding of prognosis for HT recipients who develop severe EGD requiring VA-ECMO is based largely on single-center studies with variable outcomes.[4–6] Moreover, granular data regarding VA-ECMO use at the time of HT are not well-captured in large international registries.

The objectives of this systematic review and individual patient data (IPD) meta-analysis were to (1) evaluate prognosis for patients with EGD who require VA-ECMO after HT, (2) describe the risk of major complications associated with VA-ECMO in the HT population, (3) identify factors associated with prognosis, and (4) evaluate the effect of different VA-ECMO strategies (eg, early intraoperative vs delayed postoperative cannulation on outcomes).

Methods

Data Sources and Searches

A research librarian (A.O.C.) conducted a comprehensive search strategy and searched the following databases: Ovid MEDLINE, Ovid Embase, Cochrane Database of Systematic Reviews (Ovid), and Cochrane Central Register of Controlled Clinical Trials (Ovid) through May 15, 2020 (Methods S1).

Criteria for Considering Studies

Eligible studies included nonrandomized or randomized studies of 5 or more patients, published as abstracts or full texts, in any language, after January 1, 2009. Publications were limited by date to represent more contemporary VA-ECMO strategies.[7] We included studies of adults (≥18 years) who received VA-ECMO during the index hospitalization after HT. We excluded studies on multiorgan transplant recipients, pediatric recipients, or patients for whom VA-ECMO was used after the index hospitalization for HT. We excluded other forms of MCS. Eligible studies reported on mortality at any timepoint after VA-ECMO implantation.

Study Selection

Reviewers (N.A., A.Z., T.B.) independently and in duplicate completed title, abstract and full text screening. In cases of disagreement, we reached consensus through discussion. In cases where 2 or more citations presented overlapping data, we avoided double counting patients by choosing the study with the most updated data or largest sample size.

Outcome Measures

Our outcomes of interest were mortality while on VA-ECMO support, short-term (defined as 30-day or in-hospital) mortality and 1-year mortality. Outcomes also included VA-ECMO complications: stroke (defined as hemorrhagic or ischemic stroke), bleeding (defined as any reported bleeding while supported on VA-ECMO), infection (defined as infection from any source while supported on VA-ECMO), need for dialysis, and limb ischemia (defined as tissue injury of any extremity while supported on VA-ECMO).

Data Extraction and Management

One author (N.A.) extracted aggregate data in accordance with the CHARMS-PF checklist and a second author (A.Z.) systematically checked variables for correctness.[8] In addition to key items from the checklist, we extracted donor, recipient, intraoperative, and postoperative variables.

Individual Patient Data

The rationale for the IPD meta-analysis was to evaluate the effect of VA-ECMO on mortality

accounting for individual patient characteristics and provide more consistent reporting of VA-ECMO complications. Our report followed PRISMA-IPD guidance.[9] We emailed all authors of included studies to provide de-identified IPD. One author (N.A.) reviewed all IPD and contacted study authors to reconcile any inconsistencies. We obtained local research ethics approval and approval for participating authors' institutions as per their research ethics policies.

Statistical Analyses for Overall Prognosis

Data Synthesis and Statistical Analyses. We described study population characteristics using means and standard deviations for continuous variables or counts and frequencies for categorical variables. Reviewers calculated pooled effect sizes for all studies for mortality and VA-ECMO complications with random effects models with the Freeman−Tukey double arcsine transformation using STATA (StataCorp 2019, College Station, TX). We pooled data for short-term mortality as 30 days or in-hospital, 1-year mortality, and VA-ECMO complications. If both short-term outcomes were available in a given study, in-hospital mortality was used in the meta-analysis. We compared the pooled effect sizes for IPD and non-IPD studies.

Investigation of Heterogeneity. For mortality, heterogeneity was assessed according to the following 4 subgroups: risk of bias (high vs low), publication type (full text vs abstract only), cause of EGD (PGD as per the International Society for Heart and Lung Transplantation definition vs all other definitions), and recruitment timeframe (before vs after 2009).

Assessment of Risk of Bias. Two reviewers (N.A., T.B.) independently assessed the risk of bias using a modified version of the Quality in Prognosis Studies tool.[9,10] Each domain and the overall risk of bias was assessed as "low," "moderate," or "high." If any one domain was judged high, then the overall risk of bias for a study was high.

Assessment of Publication Bias. We created funnel plots to assess for publication bias and inspected them visually as tests for publication bias may be less useful in prognostic research.[11]

Statistical Analyses for the Association Between Prognostic Factors and Mortality

Data Synthesis and Statistical Analyses. To assess prognostic factors for in-hospital and 1-year mortality, 1-stage models with single covariate interactions were created with covariates selected a priori based on clinical importance: recipient age, recipient sex, donor age, sizing by weight and predicted heart mass, pre-HT need for temporary MCS, prior sternotomy, prior left ventricular assist device use, and ischemic time. To avoid overfitting in multivariable analyses (where each study center counts as a covariate), models were created with the following covariates selected based on clinical importance: recipient age, prior sternotomy, and ischemic time. Pooled estimates for in-hospital and 1-year mortality were generated separately within each study and combined across studies using mixed effects logistic regression models to provide odds ratios. We used multiple imputation by chained equations using Rubin's rule and imputed data if fewer than 20% of values were missing.[12] If more than 20% of values were missing for any prespecified variable, the variable was excluded from the analysis. More than 20% of data were only missing for donor cause of death (21%).

Statistical Analyses for VA-ECMO−Related Interventions

Data Synthesis and Statistical Analyses. We used the RevMan Version 5.3[13] random effects models with the Mantel−Haenszel method to calculate pooled risk ratios for the effect of the above interventions on short-term mortality. From the IPD, we calculated relative risk for each individual study and then pooled the effects of the interventions from IPD and non-IPD using traditional meta-analyses techniques.

Subgroup Analyses. We analyzed the relative impact of peripheral vs central cannulation; early (intraoperative) vs late (postoperative) cannulation; use of left ventricular unloading strategies (defined as the use of an intra-aortic balloon pump, Impella, septostomy, or surgical venting) vs no left ventricular unloading strategies; and use of nitric oxide vs no nitric oxide.

Assessment of Risk of Bias. Risk of bias was assessed for effect of the intervention using the Risk Of Bias In Non-randomised Studies of Interventions tool for each outcome.[14]

Assessment of the Certainty of the Evidence

We used the GRADE framework to assess our confidence in the estimates from the gathered evidence on overall prognosis, VA-ECMO complications, prognostic factors, and VA-ECMO related interventions.[11,15] We summarized the confidence in estimates as high, moderate, low, or very low.

Results

Description of Search Results and Excluded Studies

After the removal of 496 duplicates, 2638 studies underwent title and abstract screening, of which 119 studies were included in full-text screening; of these 49 were suitable for this meta-analysis (Fig. 1). Of the 49 included studies, 15 provided IPD. Of the

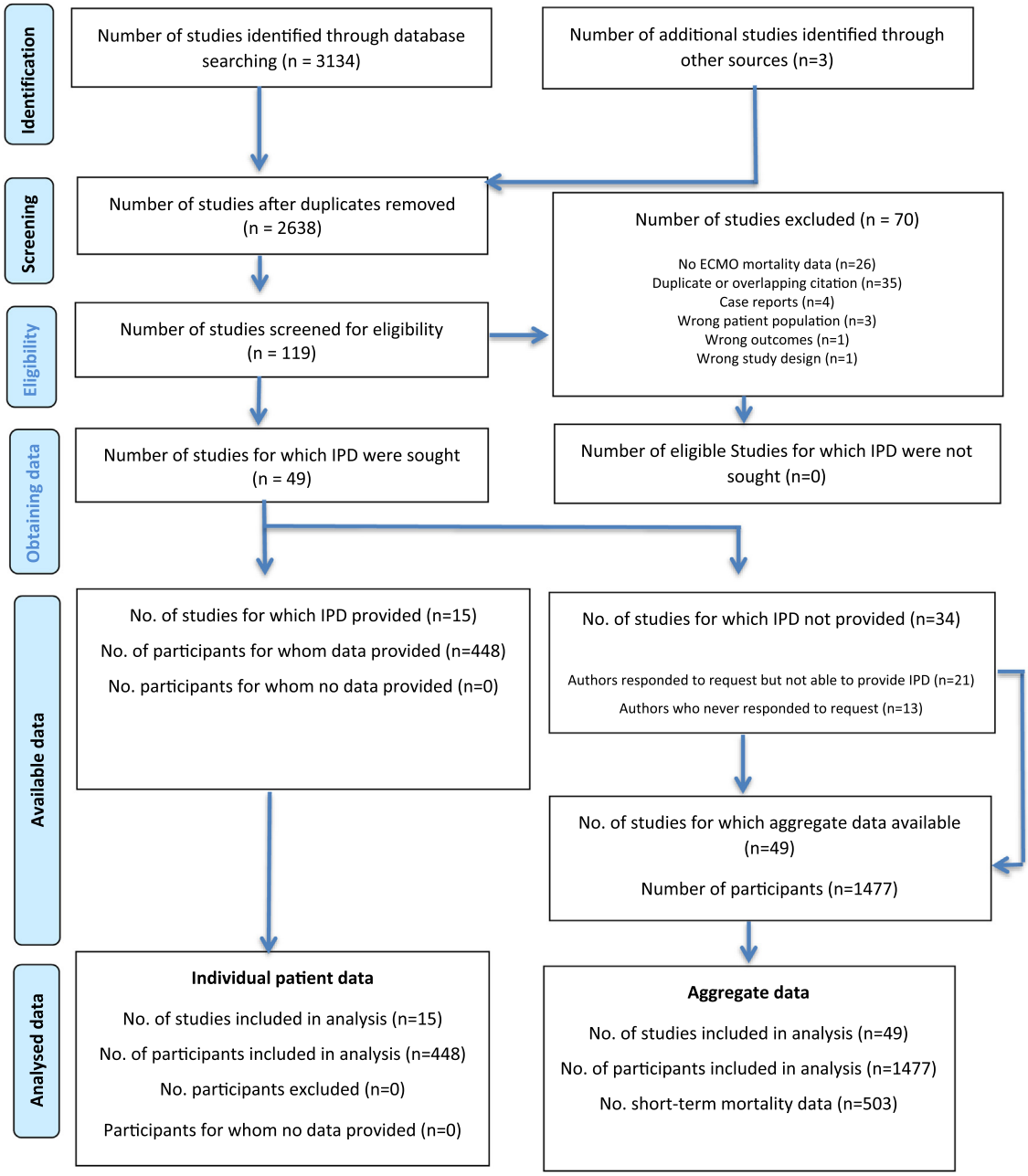


Fig. 1. PRISMA—individual patient data (IPD) flow diagram. ECMO, extracorporeal membrane oxygenation.

34 authors who did not provide IPD, 13 (38%) did not respond to our requests and 21 (62%) responded but were not able to provide the data. We excluded 70 studies, of which 35 (50%) were duplicate or overlapping citations and 26 (37%) that did not report mortality data.

Description of Included Studies

Forty-nine included studies identified 1477 patients. All 49 studies were observational cohort studies published as of 2009 and conducted between 1987 and 2018: 3 (6%) were prospective, 6 (12%) multicenter, and 27 (55%) published as full texts (Table 1, Table S1). Table 2 describes the baseline characteristics of the patients from IPD and non-IPD studies separately. IPD was provided for a total of 448 patients from 15 studies (Table S2 for additional patient characteristics). Studies providing IPD had a contemporary population (72% of patients transplanted as of 2010) with a greater proportion of patients with PGD as per the International Society for Heart and Lung Transplantation definition.[1]

Risk of Bias in Included Studies

Overall Prognosis. Most studies (77%) adequately sampled the eligible population and were at a low or acceptable risk of bias for study participation. Study

Table 1. Characteristics of Included Studies

Characteristic	Studies Included in Systematic Review ($n = 49$)	IPD Studies ($n = 15$)	Non-IPD Studies ($n = 34$)
Single center	43 (88)	14 (93)	29 (85)
Retrospective	46 (94)	14 (93)	32 (94)
Published as full text	27 (55)	10 (67)	17 (50)
Location of study			
Asia	6 (12)	0	6 (18)
Australia	3 (6)	3 (20)	0
Europe	19 (39)	6 (40)	13 (38)
North America	19 (39)	4 (27)	15 (44)
South America	2 (4)	2 (13)	0
Lower and upper recruitment timeframe	1987−2018	1997−2018	1987−2018
Primary graft dysfunction according to ISHLT definition	13 (26)	5 (33)	8 (24)

IPD, individual patient data; ISHLT, International Society for Heart and Lung Transplantation.
Continuous variables are expressed as means with standard deviations and categorical variables are expressed as counts with percentages.

attrition was judged as low or acceptable risk of bias for nearly all (98%) studies because loss to follow-up was uncommon. The overall risk of bias was low or acceptable in 36 studies (77%) that reported short-term mortality and in 16 studies (73%) that reported 1-year mortality (Fig. S1).

VA-ECMO Complications. Clear definitions were lacking; bleeding was poorly defined in 17 studies (74%), infection in 17 (74%), stroke in 15 (75%), and limb ischemia in 14 (70%). The overall risk of bias was high because of poorly defined outcome measurements and inadequate control of confounding factors (Fig. S2).

VA-ECMO−related Interventions. Most studies included all eligible patients, defined the intervention, measured an objective outcome in mortality

Table 2. Characteristics of Patients From Included Studies According to Provision of Individual Patient Data

Characteristic	IPD Studies ($n = 448$ Patients)*	Non-IPD Studies ($n = 1065$ Patients)	Non-IPD Studies Reporting Characteristic ($n = 34$ Studies)
Recipient age (years)	50 ± 13	51 ± 13	17 (50)
Female sex	24	20	14 (41)
Dilated cardiomyopathy	34	42	9 (26)
Ischemic cardiomyopathy	36	42	11 (32)
Previous sternotomy	50	51	9 (26)
Pretransplant VA-ECMO	10	28	4 (12)
Pretransplant left ventricular assist device	28	39	10 (29)
Pretransplant serum creatinine	126 ± 72	133 ± 43	8 (23)
Donor age (years)	38 ± 13	37 ± 11	12 (35)
Donor female	33	NR	NR
Cerebrovascular accident	40	38	1 (3)
Trauma	36	38	2 (6)
Anoxia	19	16	2 (6)
Ischemic time (minutes)	214 ± 88	212 ± 46	13 (38)
Cardiopulmonary bypass time (minutes)	219 ± 113	240 ± 54	7 (21)
Intraoperative ECMO	75	68	13 (38)
Postoperative ECMO	25	32	13 (38)
Central cannulation	44	28	13 (38)
Peripheral cannulation	56	72	13 (38)
IABP cotherapy	55	34	10 (29)
Nitric oxide cotherapy	79	8	3 (9)
Duration of ECMO support (days)	6.7 ± 6.1 (median 5.5, IQR 3−8)	5.0 ± 3.1	19 (56)
Hospital length of stay (days)	51 ± 56 (median 32.5, IQR 15−65)	32 ± 30	19 (56)

IABP, intra-aortic balloon pump; IQR, interquartile range; VA-ECMO, Venoarterial extracorporeal membrane oxygenation. Other abbreviations as in Table 1.
Continuous variables are expressed as means with standard deviations, and categorical variables are expressed as percentages.
*Additional IPD provided that had not been included in published studies.

and were assessed as low risk for the "participant selection," "classification of the intervention," and "outcome measurement" domains. However, the overall risk of bias for all studies was high because the domain for confounding was assessed as high risk of bias (Table S3).

Publication Bias. The funnel plot for publication bias was visually symmetrical, with an equal number of studies on either side of the summary estimate and the majority of studies falling within the 95% confidence limits, in keeping with no significant publication bias (Fig. S3).

Estimates of Prognosis

Short-term Mortality. The pooled estimate for mortality while supported on VA-ECMO was 17% (95% confidence interval [CI] 0.13−0.22) (Fig. S4) from 29 studies. The pooled estimate for 30-day or in-hospital mortality was 33% (95% CI 28%−39%, $I^2 = 75\%$) (Fig. 2) from 47 studies. Heterogeneity was not explained by subgroup analyses according to risk of bias ($P = .76$), publication type ($P = .78$), cause of EGD (ie, PGD as per the International Society for Heart and Lung Transplantation definition, $P = .72$), or recruitment timeframe ($P = .11$). There was no difference in estimates of 30-day or in-hospital mortality between IPD and non-IPD studies ($P = .91$ and $P = .17$) (Fig. S5). We are moderately confident that the true prognosis for 30-day and in-hospital mortality is close to the estimate (Table S5).

One-year Mortality. Twenty-six studies were pooled for an estimated 1-year mortality rate of 50% (95% CI 43%−57%, $I^2 = 71\%$) (Fig. S6). Heterogeneity was not explained by subgroup analyses according to risk of bias ($P = .89$), publication type ($P = .26$), cause of EGD ($P = .82$), or recruitment timeframe ($P = .23$). There was no difference in the 1-year mortality estimate between IPD and non-IPD studies ($P = .54$) (Fig. S5). Overall, we are moderately confident that the true prognosis for 1-year mortality is close to the estimate (Table S5).

VA-ECMO−related Complications. The pooled estimated risk of bleeding from 23 studies was 38% (95% CI 28%−48%) (Fig. 3). There were 23 studies that reported on VA-ECMO−related infection, with a pooled estimated risk of 21% (95% CI 14%−28%). The pooled estimated risk of limb ischemia from 20 studies was 5% (95% CI 2%−8%). Lastly, 20 studies reported on stroke, with a pooled estimated risk of 4% (95% CI 2%−7%). The pooled estimated risks were not significantly different between IPD and non-IPD studies (Fig. 3). Overall, we have moderate confidence that the true rates of VA-ECMO−related bleeding, infection, limb ischemia, and stroke are close to the estimates, although they may be different owing to differences in the outcome definition between studies and lack of adjustment for confounding variables (Table S5).

Dialysis. The pooled estimated risk of dialysis from 14 IPD studies was 60% (95% CI 49%−69%) (Fig. 3) and was significantly greater than the risk from 10 non-IPD studies (29%, 95% CI 16%−44%, $P = .001$). We have low confidence in the estimate because the true rate of dialysis may be substantially different owing to study confounding and significant differences in the estimate between IPD and non-IPD studies (Table S5).

Prognostic Factors Associated With Mortality

Short-term Mortality. Advancing recipient age (odds ratio [OR] 1.02, 95% CI 1.01−1.04, high certainty) and prior sternotomy (OR 1.57, 95% CI 0.99−2.49, high certainty) were associated with in-hospital mortality (Table 3, Table S4). Increasing donor age (OR 1.01, 95% CI 1.00−1.03, high certainty) probably increases in-hospital mortality slightly. Recipient sex, donor sex, ischemic time, and pretransplant left ventricular assist device use are factors that had little to no association with in-hospital mortality. There is low certainty in the effect estimates of the remaining prognostic factors.

One-year Mortality. Factors associated with higher 1-year mortality include advancing recipient age (OR 1.02, 95% CI 1.00−1.04, high certainty) and prior sternotomy (OR 1.56, 95% CI 1.00−2.43, high certainty). Advancing donor age (OR 1.01, 95% CI 1.00−1.03, high certainty) probably increased 1-year mortality slightly. Recipient sex, sex mismatch, ischemic time, and pretransplant left ventricular assist device had little to no effect on 1-year mortality. Evidence regarding the remaining prognostic factors has low certainty with no clear association with 1-year mortality (Table S6).

Estimates of the Effect of Interventions on Mortality

Cannulation Site. We pooled data from 509 patients from 13 IPD studies and 2 non-IPD studies. Peripheral VA-ECMO cannulation may reduce short-term mortality compared to central cannulation (relative risk [RR] 0.81, 95% CI 0.60−1.09, $I^2 = 51\%$) (Fig. 4). Overall, peripheral cannulation may reduce short-term mortality compared to central cannulation but the certainty in the evidence is low because of moderate heterogeneity between studies and imprecision (Table S7).

Timing of Cannulation. Pooling data from 11 IPD and 2 non-IPD studies of 399 patients showed a reduction in short-term death with early (ie, intraoperatively) rather than delayed (ie, postoperatively) cannulation (RR 0.76, 95% CI 0.52−1.09, $I^2 = 49\%$) (Fig. 4). Owing to confounding bias and imprecision,

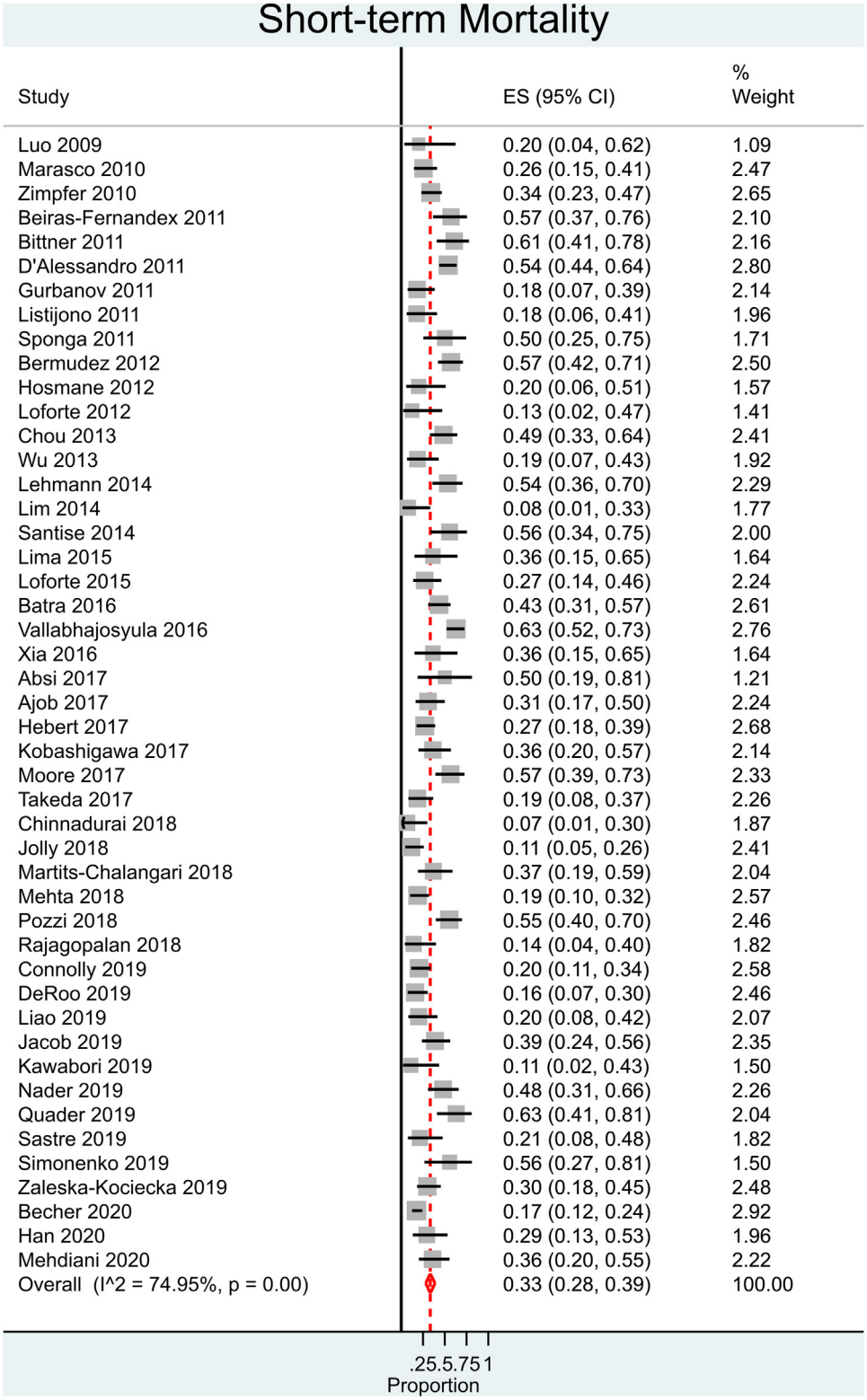


Fig. 2. Forest plot of short-term mortality expressed as a proportion. CI, confidence interval; ES, effect size.

there is low certainty evidence that early cannulation reduces the risk of short-term death.

Left Ventricular Unloading. Pooling of data from 10 IPD studies of 261 patients showed no benefit in left ventricular unloading in this population (RR 1.02, 95% CI 0.77−1.35) (Fig. 4). Intra-aortic balloon pump (55%), surgical venting (44%), and Impella (1%) were strategies used for left ventricular

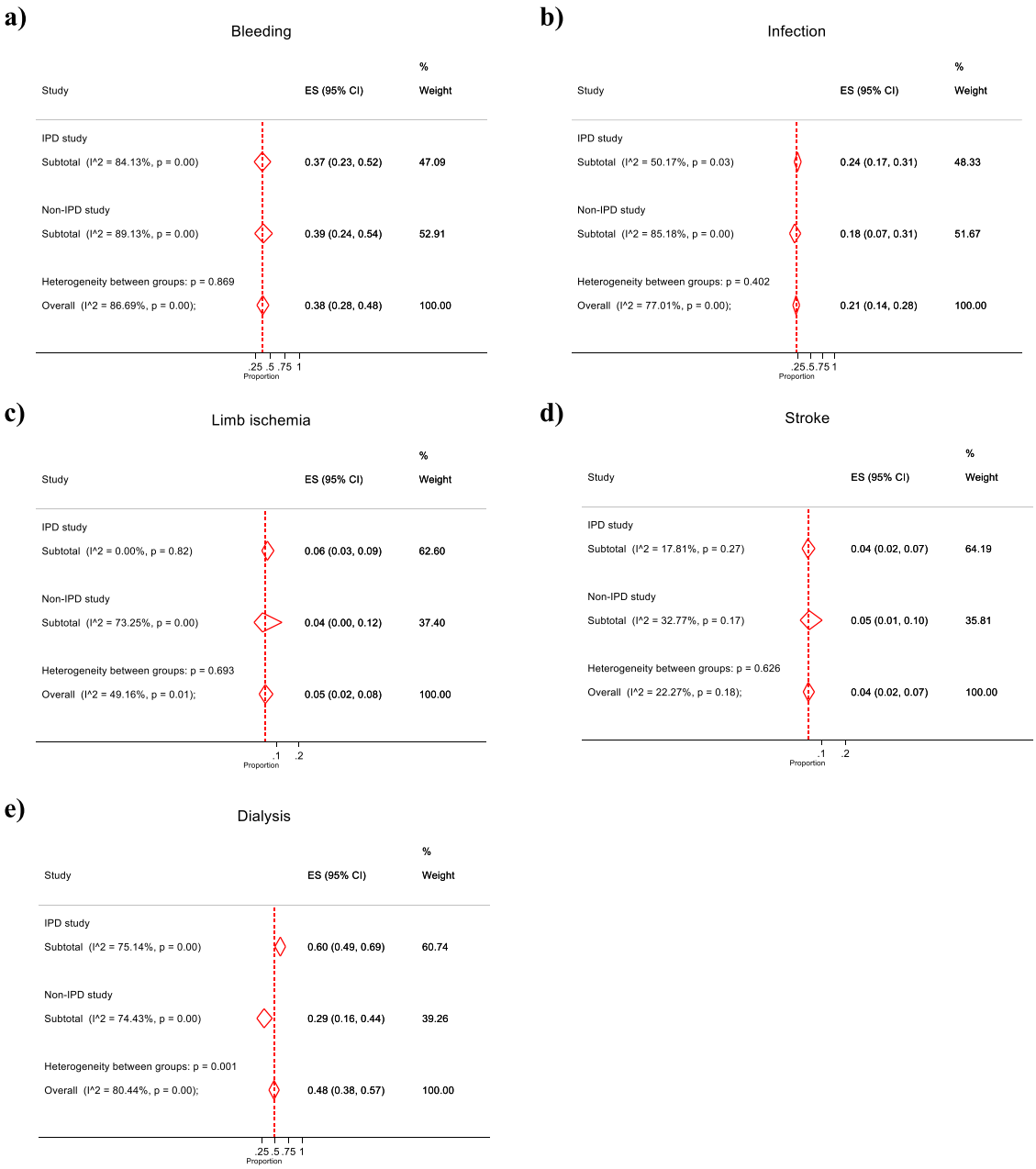


Fig. 3. Forest plot of venoarterial extracorporeal membrane oxygenation (VA-ECMO) complications according to studies that did and did not provide individual patient data for (**a**) bleeding, (**b**) infection, (**c**) limb ischemia, (**d**) stroke, and (**e**) dialysis. Abbreviations as in Figs. 1 and 2.

unloading. There was no heterogeneity between studies ($I^2 = 0\%$). Owing to confounding bias and low event rates, the effect of left ventricular unloading strategies on mortality is uncertain.

Use of Nitric Oxide. There were 5 IPD studies of 80 patients suitable to evaluate the effect of nitric oxide cotherapy on in-hospital mortality. Pooling of data from these 5 studies suggested no benefit when nitric oxide was used (RR 1.28, 95% CI 0.86−1.92) (Fig. 4). The heterogeneity between studies was not important ($I^2 = 6\%$). The evidence is very uncertain about the effect of nitric oxide on in-hospital mortality.

Discussion

Main Study Findings

In this systematic review of patients requiring VA-ECMO for EGD from 49 studies, we report a short-term mortality estimate of 33% and by 1 year of 50% (Fig. 5). VA-ECMO−related bleeding and infection occurred in 38% and 21% of patients, respectively; however, rates of stroke and limb ischemia were low. We are moderately confident in these estimates and found no difference in estimates between studies that did and did not provide IPD. We identified recipient age and prior sternotomy as

Table 3. Summary of Findings for Factors Associated With In-hospital Mortality

Prognostic Factor	Study Results Based on 448 Patients From 15 Studies	Absolute Effect Estimates	Certainty in Effect Estimates (Quality of Evidence)	Plain Text Summary
Recipient age (per 1-year increase)	Odds ratio 1.02 (95% CI 1.01−1.04)	Difference: 7 more deaths per 1000 (2−10 more per 1000)	High	Advancing recipient age slightly increases in-hospital mortality
Recipient sex (female vs male)	Odds ratio 1.06 (95% CI 0.65−1.72)	Difference: 14 more deaths per 1000 (82 fewer to 135 more per 1000)	Moderate owing to serious imprecision	Recipient sex makes little to no difference on in-hospital mortality
Donor age (per 1-year increase)	Odds ratio 1.01 (95% CI 1.00−1.03)	Difference: 2 more deaths per 1000 (0−7 more per 1000)	High	Increasing donor age probably increases in-hospital mortality slightly
Donor sex (female vs male)	Odds ratio 0.85 (95% CI 0.54−1.35)	Difference: 39 fewer deaths per 1000 (112 fewer to 75 more per 1000)	Moderate owing to serious imprecision	Donor sex makes little to no difference on in-hospital mortality
Female donor to male recipient (yes vs no)	Odds ratio 0.54 (95% CI 0.30−0.97)	Difference: 138 fewer deaths per 1000 (7−186 fewer per 1000)	Low owing to serious imprecision and risk of confounding bias	Sex mismatch may be associated with in-hospital mortality, but our certainty in the estimate is limited
Ischemic time (per minute increase)	Odds ratio 1.00 (95% CI 0.99−1.00)	Difference: 0 deaths per 1000 (2 fewer to 0 more per 1000)	High	Ischemic time makes little to no difference in-hospital mortality
Donor−recipient weight ratio	Odds ratio 1.92 (95% CI (0.74−4.98)	Difference: 160 more deaths per 1000 (59 fewer to 360 more per 1000)	Low owing to serious imprecision and inconsistency	Donor−recipient weight ratio may or may not affect in-hospital mortality, but our certainty in the estimate is limited
Donor−recipient PHM ratio	Odds ratio 1.57 (95% CI 0.53−4.71)	Difference: 110 more deaths per 1000 (115 fewer to 350 more per 1000)	Low owing to serious imprecision and inconsistency	Donor−recipient PHM ratio may or may not affect in-hospital mortality but our certainty in the estimate is limited
Pretransplant temporary MCS (yes vs no)	Odds ratio 1.13 (95% CI 0.39−3.35)	Difference: 29 more deaths per 1000 (157 fewer to 286 more per 1000)	Low owing to serious imprecision and inconsistency	Pretransplant temporary MCS may have little to no effect on in-hospital mortality, but our certainty is limited
Pretransplant LVAD (yes vs no)	Odds ratio 0.95 (95% CI 0.65−1.38)	Difference: 12 fewer deaths per 1000 (82 fewer to 80 more per 1000)	Moderate owing to serious imprecision	Pretransplant LVAD may have little to no effect on in-hospital mortality
Prior sternotomy (yes vs no)	Odds ratio 1.57 (95% CI 0.99−2.49)	Difference: 96 more deaths per 1000 (2 fewer to 223 more per 1000)	High	Prior sternotomy probably increases in-hospital mortality
Pretransplant dialysis (yes vs no)	Odds ratio 1.38 (95% CI 0.65−3.02)	Difference: 77 more deaths per 1000 (82 fewer to 265 more per 1000)	Low owing to serious imprecision and inconsistency	Pretransplant dialysis may or may not affect in-hospital mortality but our certainty in the estimate is limited

CI, confidence interval; LVAD, left ventricular assist device; MCS, mechanical circulatory support; PHM, predicted heart mass.

prognostic factors associated with short-term and 1-year mortality. Peripheral cannulation and early intraoperative cannulation may decrease short-term mortality compared with central cannulation and late postoperative cannulation, respectively, based on low certainty evidence.

Comparison With Other Studies

In comparison with other causes of cardiogenic shock that require VA-ECMO support, the use of VA-ECMO in our population is consistent with previous reports of better short-term survival.[16] The advantage of our systematic review is the inclusion of more studies than in previous reports, with doubling of the patients evaluated (695 vs 1447), leading to more precise estimates of prognosis.[16,17] In addition, we provide estimates of intermediate-term survival, which are not-well reported for this population.[18] Estimated survival to 1 year after HT in our review was 50%, which is better than all-comers with cardiogenic shock who require VA-ECMO.[18] Reasons

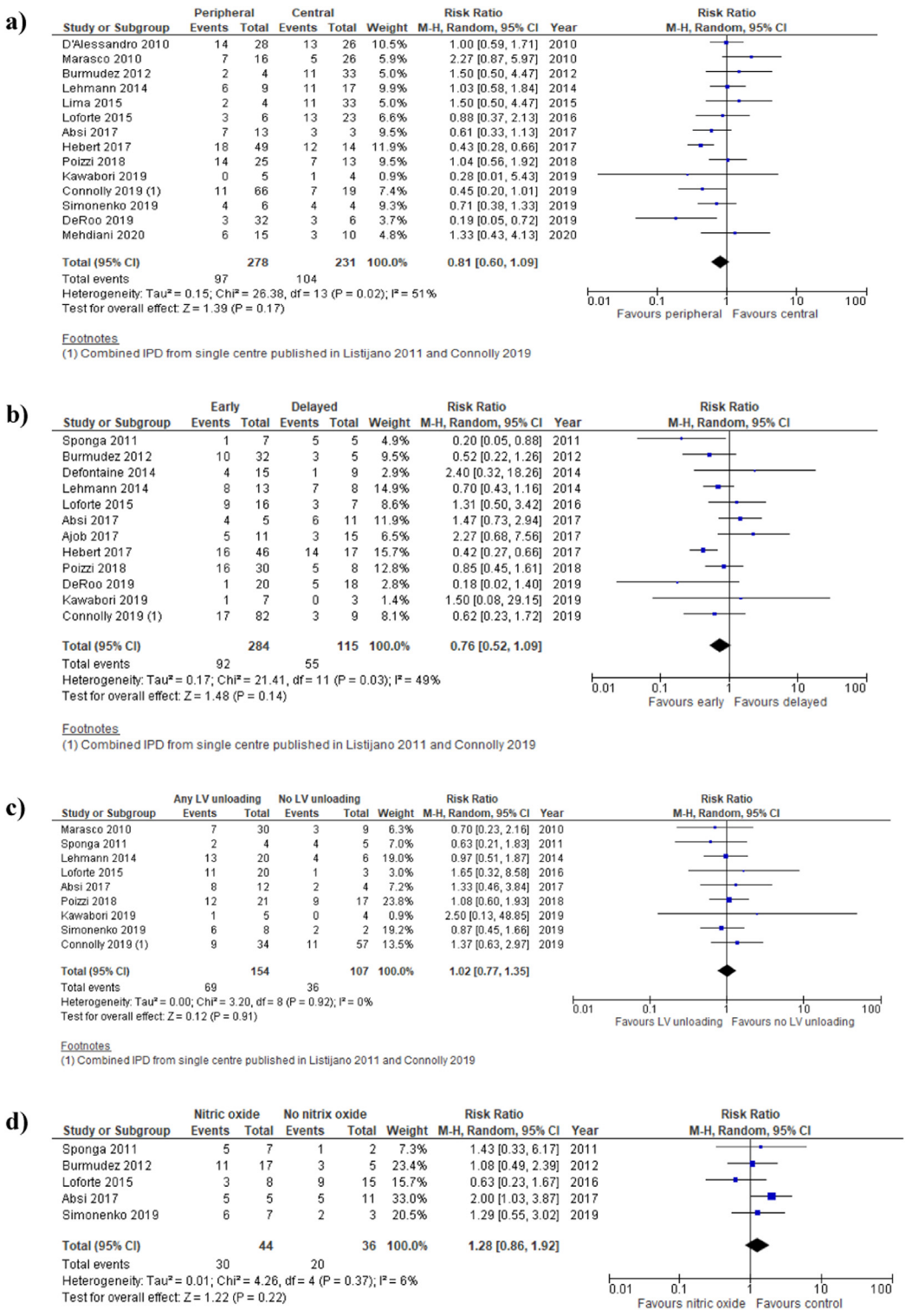


Fig. 4. Forest plot of (**a**) peripheral vs central cannulation, (**b**) early intraoperative vs delayed postoperative cannulation, (**c**) left ventricular (LV) unloading, and (**d**) nitric oxide cotherapy on short-term mortality. Abbreviations as in Fig. 2.

for greater survival may be related to the younger age of transplant recipients, the higher likelihood of recovery of ventricular function, and lower rates of cardiopulmonary resuscitation at the time of ECMO cannulation.[16,19]

Implications of Prognostic Factors on Mortality

Although several recipient, donor, and perioperative factors have been associated with developing PGD of any severity, less is known about factors that impact mortality in severe cases in which MCS

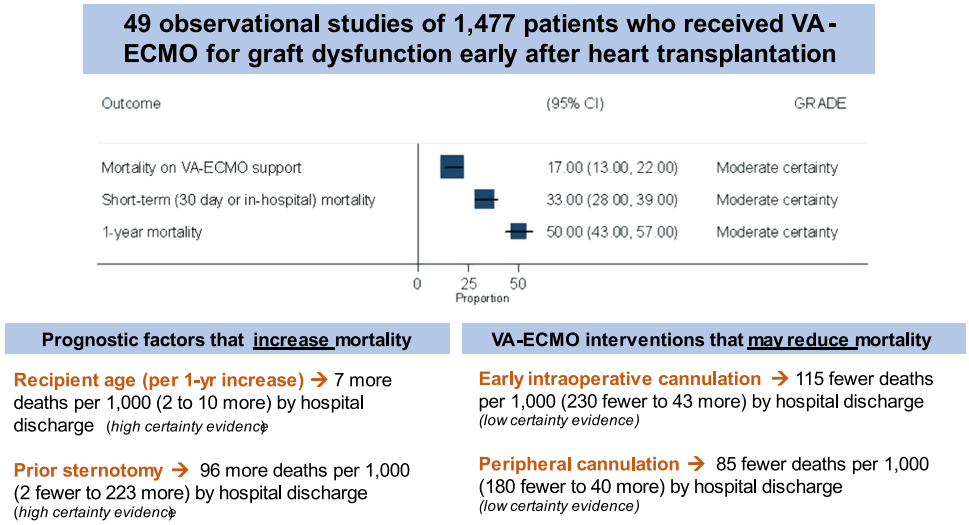


Fig. 5. Visual Take Home Graphic. Summary of findings for mortality, and prognostic factors and VA-ECMO-related interventions that impact mortality. Abbreviations as in Figs. 2 and 3.

is needed.[20] The association between recipient age and mortality appears modest, but for every 1-year increase in recipient age, 7 more people per 1000 died before hospital discharge. Pre-HT temporary MCS including VA-ECMO did not impact mortality, which is surprising given the association between pre-HT temporary MCS and lower survival after HT.[21] Patients supported with VA-ECMO pre-HT are dying more after HT, but for various reasons not limited to severe EGD requiring VA-ECMO support. For example, in a recent United Network for Organ Sharing analysis of 177 patients supported with VA-ECMO pre-HT, 16 (9%) died of graft failure.[22] In contrast, prior sternotomy was an important prognostic factor associated with 96 more deaths per 1000 before hospital discharge. As a marker of prior cardiac surgery including congenital surgery, previous sternotomy may reflect a more complicated reoperation, longer cardiopulmonary bypass times, and the need for more perioperative transfusions.

Lastly, donor age may have a slight impact on mortality, although ischemic time did not. In this analysis, ischemic time was on average 3.5 hours, which is below the 4- to 6-hour cut-offs associated with poor outcomes after HT and may explain the lack of association with mortality in this cohort or may reflect noted interactions between donor age and ischemic time.[23] A more advanced donor age reflects an older graft, which may have less cardiac reserve, a lower ability to accommodate catecholamine shifts, and may not tolerate the hemodynamic consequences of VA-ECMO support.[24] Importantly, other donor-related factors such as donor sex, sex mismatch, and sizing did not have a deleterious impact on survival for recipients supported with VA-ECMO.

Implications of VA-ECMO–related Complications

Bleeding and a need for dialysis were common complications in our study and occurred at similar rates as in non-HT populations.[25,26] Although we have low certainty in the dialysis estimate, there is also heterogeneity in the reported rates of dialysis in the literature, and it may reflect differences in patient or center characteristics.[25] Infection risk in the HT population was reassuringly similar to rates reported in nonimmunosuppressed populations.[27] Similarly, estimates of stroke and limb ischemia in our study were comparable with rates across heterogenous groups of patients.[28]

Implications of VA-ECMO–related Interventions

As the use of VA-ECMO increases, there is growing interest in optimizing the decision-making and management of patients supported with this form of temporary MCS. Central vs peripheral cannulation is an important consideration in VA-ECMO use after cardiac surgery, with advantages and disadvantages to both techniques. Although central cannulation is practical because the cannulas for cardiopulmonary bypass can be used, it is not necessarily the more advantageous approach.[26,29] In a registry analysis of patients with shock after cardiotomy, central cannulation was associated with a lower survival.[30] We found peripheral cannulation may decrease short-term mortality, which may reflect lower rates of bleeding and infection than would be encountered with central cannulation.

The timing of temporary MCS considers the risk of unnecessarily exposing a patient to complications associated with MCS against the deleterious consequences of ongoing low cardiac output to end-

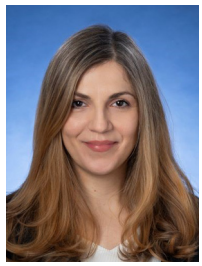
organ perfusion. This decision may be particularly challenging in EGD, where graft loss is possible but so is recovery in ventricular function. In some refractory cardiogenic shock populations, the early introduction of temporary MCS may be associated with improved survival.[31,32] Our findings raise the possibility that early intraoperative cannulation is associated with fewer deaths. Because research in this area is limited, ongoing prospective evaluation for optimal timing of VA-ECMO cannulation is warranted.

Strengths and Limitations

Our review process was broad and extensive to account for all eligible studies. We evaluated the largest cohort of HT patients supported with VA-ECMO to our knowledge with granular data on VA-ECMO–related and HT-related variables. However, there are limitations. Although we could not acquire IPD for all the identified studies, there was no difference in the estimates of mortality between the IPD and non-IPD studies and no difference in our confidence in overall prognosis. It is possible that additional patients may have strengthened the association between certain prognostic factors and mortality, but event rates from the IPD were high (eg, 203 mortality events by 1 year) and the likelihood of changing the absolute direction of associations low. We did not restrict studies based on prespecified definitions for VA-ECMO complications; however, we identified that clear definitions for VA-ECMO complications are lacking and needed to ensure consistent outcome measures are available for future research in this area. Although we were able to evaluate several important prognostic factors associated with the development of severe graft dysfunction necessitating VA-ECMO, other factors that are increasingly associated with PGD, such as amiodarone use,[33] were not well-reported and, therefore, not evaluated, but should be included in prospectively collected registries. Last, we limited our systematic search to publications of 5 or more patients, to exclude case series and studies from small volume centers because VA-ECMO center volume has been associated with mortality.[34]

Conclusions

In the largest systematic review of prognosis in patients who require VA-ECMO early after HT for severe graft dysfunction, most patients are weaned from support, although approximately one-third do not survive to hospital discharge and nearly one-half do not survive to 1 year. Prior recipient sternotomy and recipient age are factors that negatively impact survival and may inform decision-making at the time of transplant. Early intraoperative cannulation and peripheral cannulation are practices that may improve survival, however further research is needed to improve the certainty in the evidence pertaining to VA-ECMO techniques in this population.



Brief Lay Summary

Early graft dysfunction (EGD) refers to the failure of a donor heart soon after it is transplanted into a recipient. When severe, the management of EGD may include the use of a temporary heart–lung machine called venoarterial extracorporeal membrane oxygenation (VA-ECMO) to support the circulation. We reviewed studies reporting rates of death in recipients who required VA-ECMO for EGD and found that although most patients can be separated successfully from this machine, approximately one-third die in the short term and just under one-half die by 1 year after transplant. Recognizing ways to improve survival before and after these patients are separated from VA-ECMO will be important for future work.

Patient Applications

- Although most patients who require VA-ECMO early after HT are weaned from support, one-third of these recipients do not survive to hospital discharge and one-half do not survive to 1 year. This prognostic information is important information for patients who experience severe EGD necessitating VA-ECMO, their families, and the medical community.
- After adjusting for ischemic time, prior sternotomy and recipient age are factors associated with decreased survival.
- Early intraoperative cannulation and peripheral cannulation are VA-ECMO strategies that may improve survival, but warrant further study.

Conflict of Interest

The authors report no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.11.011.

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