EXTRACORPOREAL MEMBRANE OXYGENATION FOR EARLY GRAFT DYSFUNCTION AFTER HEART TRANSPLANTATION

EXTRACORPOREAL MEMBRANE OXYGENATION FOR EARLY GRAFT DYSFUNCTION FOLLOWING HEART TRANSPLANTATION: A SYSTEMATIC REVIEW AND INDIVIDUAL PATIENT DATA META-ANALYSIS

BY: NATASHA ALEKSOVA, BSc MD

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AUTHOR: Natasha Aleksova, BSc MD

SUPERVISOR: Dr. Gordon Guyatt, MD, MSc

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LAY ABSTRACT:

Early graft dysfunction (EGD) refers to the failure of a donor heart soon after it is transplanted into a recipient. EGD is a major cause of early complications and death in heart transplant recipients. The management of severe EGD may include the use of a temporary heart-lung machine called veno-arterial extracorporeal membrane oxygenation (VA-ECMO), which supports the circulation while the transplanted heart recovers. In our review of studies reporting rates of death in recipients who required VA-ECMO for EGD, we found that approximately one-third die in the short-term and just under half die by one-year after transplant. The most common complications while supported on VA-ECMO were bleeding, infection and need for dialysis. Older recipient, donor age, and having a prior sternotomy were factors associated with lower survival to hospital discharge. Connecting to peripheral blood vessels rather than central ones and earlier use of VA-ECMO support may be associated with lower risk of death. Our findings are important because we demonstrate that prognosis in the first year after HT for these patients is not as favorable as is commonly believed. Strategies at the time of VA-ECMO use may improve survival but require further study.

ABSTRACT:

Background: Early graft dysfunction (EGD) is a major cause of early morbidity and mortality following heart transplantation (HT). The management of severe EGD often includes the use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Studies evaluating the effectiveness of VA-ECMO are primarily retrospective single centre studies with variable results.

Objectives: The objectives of this systematic review and individual patient data (IPD) meta-analysis are to appraise the available evidence to: 1) evaluate overall prognosis (30-day mortality, in-hospital mortality, 1-year mortality), 2) characterize rates of other major VA-ECMO complications, 3) identify factors associated with prognosis (in-hospital mortality, 1-year mortality) and 4) compare the effect of different ways of delivering VA-ECMO (e.g., peripheral vs. central cannulation, early intraoperative vs. delayed postoperative cannulation) on outcomes in adult HT recipients who developed severe EGD and received VA-ECMO

Search methods: We searched Ovid MEDLINE, Ovid Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Clinical Trials from January 1, 2009 to May 15, 2020. We included randomized and non-randomized studies published in any language, as abstracts or full texts that included adults (≥18 years) who received VA-ECMO during their index hospitalization after HT and reported on mortality at any timepoint.

Data collection and analysis: We assessed risk of bias using QUIPS for objectives 1-3 and ROBINS-I for objective 4. One reviewer completed data extraction and a second reviewer verified. Authors of each identified study from the systematic review received invitations to participate in the IPD meta-analysis. We pooled study level data for 30-day mortality, in-hospital mortality, 1-year mortality and VA-ECMO complications using random-effects models with the *metaprop* command on STATA (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.). To identify prognostic factors, we analysed IPD using a mixed effects logistic regression with a random effects term for each IPD study. We calculated summary risk ratios using random effect models for the effect of the following interventions on survival to hospital discharge: central vs. peripheral cannulation, intraoperative (early) vs. postoperative (delayed) cannulation, LV unloading vs. no LV unloading, nitric oxide vs. no nitric oxide while on VA-ECMO support. We assessed the certainty in the evidence using the GRADE framework.

Results: We included 49 observational studies of 1,477 patients of which 15 studies of 448 patients provided IPD. In addressing prognosis using QUIPS, most studies (79%) proved at low or acceptable overall risk of bias. There were no important differences in short-term or 1-year mortality estimates between IPD and non-IPD studies. We are moderately certain in the short-term mortality estimate of 33% (95%CI: 27%, 39%) and 1-year mortality estimate of 50% (95%CI: 43%, 57%). With moderate certainty, estimates of bleeding and sepsis/infection while on VA-ECMO support were 38% (95%CI: 28%, 48%) and 21% (95%CI: 14%, 28%) respectively. Three factors were

associated with increased short-term mortality with high certainty: recipient age (OR 1.02, 95% CI: 1.01-1.04), donor age (OR 1.01, 95% CI 1.00-1.03) and prior sternotomy (OR 1.57, 95%CI 0.99-2.49). Lastly, there is very low certainty evidence that VA-ECMO strategies of early intraoperative cannulation and peripheral cannulation reduce the risk of in-hospital mortality.

Conclusions: One third of patients who receive VA-ECMO for EGD do not survive to hospital discharge, and nearly half do not survive to 1 year after HT. Improving outcomes in this patient population will require careful consideration of recipient factors such as age and prior sternotomy and further research on optimal VA-ECMO strategies.

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Lastly, I am grateful for the support of my family as I juggled not only my educational commitments, but also the start of my professional career and parenthood. Thank you to my parents, to Nick and especially to Max.

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LIST OF ABBREVIATIONS

EGD: early graft dysfunction

HT: heart transplantation

ISHLT: International Society of Heart and Lung Transplantation

IPD: individual patient data

MCS: mechanical circulatory support

PGD: primary graft dysfunction

VA-ECMO: veno-arterial extracorporeal membrane oxygenation

DECLARATION OF ACADEMIC ACHIEVEMENT

I was the main contributor of this systematic review and individual patient data meta-analysis, which was completed under the guidance and supervision of Dr. Gordon Guyatt. I devised the idea for this project, was involved in the development of the search strategy, and completion of the systematic search including abstract and full texting screening. I also completed data extraction, data analysis and manuscript drafting. Lastly, I contacted all study authors for individual patient data and completed data transfer agreements as necessary. I would like to acknowledge the involvement of Tayler Buchan in abstract and full text screening, as well as in the risk of bias assessment which was conducted in duplicate. Alice Zhu was involved in abstract and full text screening and checking data extraction for correctness. Farid Foroutan was instrumental to this project and assisted in my understanding of the statistical software, STATA, so that I was then able to conduct necessary statistical analyses for the individual patient data meta-analysis portion of this project.

INTRODUCTION

Early graft dysfunction (EGD) is common and is a major cause of mortality following heart transplantation (HT). Reported rates vary from 8 to 20%, and EGD accounts for nearly two-thirds of deaths in the first 30 days after HT(1). EGD can present intra-operatively or during the first few days of the post-operative period. EGD is classified as primary (referred to as primary graft dysfunction, PGD) or secondary to a specific etiology such as sepsis, hyperacute rejection or surgical complications(1). The pathophysiology of PGD remains unclear, but risk factors include donor factors, organ procurement factors such as ischemic time and injury related to reperfusion of the organ, and recipient factors such as the need for pre-HT mechanical circulatory support (MCS)(1).

The definition of PGD was not standardized until a recent consensus conference of the International Society of Heart and Lung Transplantation (ISHLT) in 2014(1), which defined PGD as any degree of graft dysfunction in the first 24 hours post-HT classifying it into three categories of LV dysfunction: mild, moderate, and severe. Severe PGD often requires short-term MCS, and its success depends on timing of initiation of support, pre-existing patient comorbidities and severity of peripheral organ hypoperfusion.

In recent years, one of the most widely used forms of short-term MCS has been veno-arterial extracorporeal membrane oxygenation (VA-ECMO)(2). VA-ECMO has many advantages over other MCS because it can quickly provide bi-ventricular support, as is often needed in EGD (3). Furthermore, in patients with concomitant respiratory failure, an oxygenator can be added to the VA-ECMO circuit to provide respiratory support. VA-ECMO cannulation can

be central via a sternotomy or peripheral via peripheral vessels, and it can occur intra-operatively or early during the post-operative period.

Whether primary or secondary in etiology, early graft dysfunction may be a severe, life-threatening but reversible process, and VA-ECMO can be used as a bridge to recovery or less commonly re-HT. Due to the significant risks and cost associated with VA-ECMO, timely decision-making and the availability of an experienced team may favourably impact outcomes after VA-ECMO implant. Our current understanding of prognosis for HT recipients who develop severe EGD requiring VA-ECMO is based largely on single centre studies with variable outcomes(4–6). Moreover, granular data regarding temporary MCS at the time of HT, short-term outcomes and complications are not well captured in large international registries such as the International Society of Heart and Lung Transplantation registry.

PICOTS study question

In this systematic review and individual patient data (IPD) meta-analysis, the primary PICOTS question is: "In adult HT recipients who develop early graft dysfunction and require VA-ECMO, what is their prognosis in terms of survival to 30 days, hospital discharge and 1 year after heart transplantation?"

Study objectives

In keeping with the PROGRESS (PROGnosis RESearch Strategy) framework(7), the objectives of this systematic review and IPD meta-analysis were to:

1) evaluate 30-day, in-hospital and 1-year mortality for patients with EGD who require VA-ECMO after HT;
2) describe the risk of major complications associated with VA-ECMO (bleeding, infection, limb ischemia, stroke and need for dialysis) in the HT population;
3) identify donor and recipient factors associated with prognosis;
4) compare the effects of different treatment options for the provision of VA-ECMO support (e.g., early intraoperative vs. delayed postoperative cannulation, peripheral vs. central cannulation) on outcomes.

METHODS

PART I: DATA SEARCH, SCREENING, AND EXTRACTION

Data sources and searches

A research librarian (AOC) created a comprehensive search strategy in consultation with the first author (NA) to identify studies on HT and VA-ECMO published since January 1, 2009 (Appendix 1.1). On May 15, 2020, we searched the following databases: Ovid MEDLINE, Ovid Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Clinical Trials. We identified additional studies by searching bibliographic references of key articles and previously published meta-analyses(8).

Criteria for considering studies

Types of studies: We specified the types of studies eligible for this systematic review a priori in the study protocol (Appendix 1.2). Eligible studies included non-randomized (controlled observational studies or case-series) or randomized studies of ≥ 5 patients, published as abstracts or full texts, in any language, after January 1, 2009. Abstracts without full publications were eligible if they provided sufficient information to characterize the population and mortality. The decision to limit publications by date was to represent more contemporary VA-ECMO strategies and management of HT patients(9,10).

Type of participants: We included studies of adult (≥18 years) HT recipients who received VA-ECMO during the index hospitalization after HT. We excluded studies on multi-organ transplant recipients, pediatric recipients, or HT patients for whom VA-ECMO was used after the index hospitalization for HT. We excluded other forms of MCS such as veno-venous-ECMO (VV-ECMO).

Type of outcome measures: Eligible studies reported on mortality at any timepoint after VA-ECMO implantation.

Study selection

Reviewers (NA, AZ, TB) independently and in duplicate completed title and abstract screening and full text screening using the reference management software Covidence (Veritas Health Innovation, Melbourne, Australia). Each reviewer piloted a study eligibility form for the first 50 citations screened to ensure the selection process was applied correctly (Appendix 1.3). In cases of disagreement during full-text screening, 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. We documented the reason for exclusion for all studies excluded at the full-text screening phase.

Outcome measures

We included outcomes important to short-term and long-term prognosis in this patient population: short-term mortality (defined as 30-day or in-hospital mortality) and long-term mortality (defined as 1-year mortality). We pooled 30-day or in-hospital mortality as they were felt to be comparable outcomes. If both outcomes were available in a given study, in-hospital mortality was used in the study level data meta-analysis. Outcomes also included clinically relevant VA-ECMO complications: stroke (defined as either 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), and limb

ischemia (defined as any reduction in perfusion leading to tissue injury of any extremity while supported on VA-ECMO).

Data extraction and management

One author (NA) extracted study level data into an Excel worksheet and a second author (AZ) systematically checked important variables (number of patients on VA-ECMO, number of patients that died at different timepoints) for correctness. In addition to the key items from the **CH**ecklist for critical **A**ppraisal and data extraction for systematic **R**eviews of prediction **M**odelling **S**tudies – **P**rognostic **F**actor (CHARMS-PF) checklist, data extracted included recruitment time frame, number of transplants and ECMO during the recruitment time frame, patient age and sex, mechanical ventilation, prior HT, prior sternotomy, prior left ventricular assist device, prior ECMO, pre-transplant serum creatinine and peak lactate immediately prior to ECMO implant, timing of ECMO implant in relation to HT, number of deaths at different time points and follow up times (e.g. mortality during ECMO support, mortality before hospital discharge and 1-year mortality). We also collected information on the use of co-interventions including their timing/initiation, duration of ECMO support and its complications, including need for dialysis, bleeding requiring re-operation, limb ischemia with compartment syndrome or requiring amputation, embolic or hemorrhagic stroke, and infection, and the number of patients who required re-transplantation and/or ventricular assist device after ECMO. Lastly, we abstracted data on HT-related variables, including donor age, sex, height and weight, donor cause of death if known, donor smoking, donor hypertension, donor diabetes, donor drug use, donor LVEF, donor use of inotropes, ischemic time, use of induction immunosuppression, and graft function after ECMO decannulation.

Individual patient data

Rationale for IPD meta-analysis: In our aggregate study level data meta-analysis, we identified significant between study heterogeneity, poor reporting of secondary outcomes and a large proportion of studies published only as abstracts with missing or incomplete information. We used meta-regression to explore the impact of aggregated covariates on short-term mortality, but this suffers from risks of confounding and ecological bias(11). For these reasons, we wanted to better account for the between study heterogeneity observed in our study level data meta-analysis, evaluate the effect of VA-ECMO on mortality accounting for individual patient characteristics, and provide updated and more comprehensive information including longer follow up and more consistent reporting of VA-ECMO complications.

Obtaining individual patient data: We requested all authors of studies included in the study level data meta-analysis to provide de-identified IPD. Appendix 2.1 includes the study invitation e-mail template. We contacted the corresponding author for each study by e-mail correspondence on a maximum of 3 separate occasions, 2 weeks apart. If the corresponding author did not respond to our request after 3 attempts, we then contacted the senior author or first author (if not corresponding author) in the same fashion. We sought to collect data on all patients as described in the identified studies of study level data and if feasible, data as described in our data collection form to capture unreported outcomes and other unpublished details (Appendix 2.2).

Assessment of IPD integrity and quality: One author (NA) reviewed all data items included from the IPD for inconsistencies and contacted study authors to reconcile any inconsistent, incorrect, or missing data.

Data reporting: Our report followed PRISMA-IPD guidance(12).

Ethics approval: To transfer de-identified IPD from the participating authors' institutions, we obtained research ethics approval at Toronto General Hospital, University Health Network. We also obtained research ethics approval for participating authors' institutions as per local research ethics policies.

PART II: STATISTICAL ANALYSES, RISK OF BIAS AND GRADE FOR OVERALL PROGNOSIS

The following section describes the methods used to evaluate the first and second study objectives of this project, pertaining to overall prognosis and major complications for patients with EGD who require VA-ECMO after HT.

Subgroup analysis and investigation of heterogeneity of study level data

For short-term and long-term mortality, heterogeneity was assessed according to the following 4 subgroup analyses based on study characteristics: risk of bias (high vs. low), publication type (full text vs. abstract only), cause of EGD (PGD as per the ISHLT definition vs. all forms of EGD), and recruitment timeframe (before vs. after 2009). Recruitment timeframe refers to the era in which patients received VA-ECMO, either before or after 2009, and does not refer to the publication date of the study. Meta-regression was performed on study level data, evaluating the relationship between short-term mortality and the following covariates: mean age, sex (proportion female), proportion of patients requiring pre-transplant temporary MCS, mean ischemic time, and the proportion of patients requiring the use of any LV unloading strategy.

Assessment of risk of bias

Two reviewers (NA, TB) independently assessed the risk of bias for each of the included studies using a modified version of the QUIPS (Quality in Prognosis Studies) tool using the following domains: study participation (consecutive or random patient selection), study

attrition (complete follow up), study confounding and outcome measurement (objective and unbiased assessment).[10, 11] 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. If a domain was judged "moderate" and there were no domains judged "high" risk of bias, then the overall risk of bias for a study was moderate. If all domains were judged low risk of bias, then the overall risk of bias was low. For studies that did not include model development or regression analysis, we adjudicated the domain 'statistical analysis/reporting' as "not applicable". Reviewers resolved disagreements by consensus or through discussion with a third reviewer (AC).

Assessment of publication bias

We created funnel plots to assess for publication bias and inspected them visually and using Egger's test for asymmetry for small-study effects. (13)

Data synthesis and statistical analysis

We described study population characteristics using means and standard deviations for continuous variables or counts and frequencies for categorical variables for study level data and separately for studies that provided IPD. Reviewers calculated pooled effect sizes for study level data for short-term mortality at 30 days or mortality before hospital discharge, for long-term mortality at 1 year and for VA-ECMO complications with random-effects models with Freeman-Tukey Double Arcsine Transformation using STATA Version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Specifically, we used the STATA command *metaprop* to pool effect sizes described as proportions(14).

We compared the pooled effect sizes for 30-day mortality, in-hospital mortality, 1-year mortality and VA-ECMO complications for IPD and non-IPD (i.e., study level data that did not provide IPD) data using the *metaprop* STATA command. Since IPD provided data at multiple timepoints, we pooled short-term mortality defined as 30-day and in-hospital mortality separately for the purposes of comparing to non-IPD. A statistical plan was agreed upon before starting IPD analysis (Appendix 2.3).

Assessment of the certainty of the evidence

GRADE guidance provided the approach to assess our confidence in the estimates from the gathered evidence on overall prognosis and VA-ECMO complications and to present it in a summary of findings table(15). Risk of bias, inconsistency, imprecision, indirectness, and publication bias were the domains considered in the assessment of the certainty of the evidence. We summarized the confidence in estimates as high, moderate, low, or very low.

PART III: STATISTICAL ANALYSES, RISK OF BIAS AND GRADE FOR PROGNOSTIC FACTORS

The following section describes the methods used to evaluate the third study objective, pertaining to the identification of factors associated with prognosis.

Data synthesis and statistical analysis

The one-step and two-step approach are two ways to pool data in an IPD meta-analysis. In the one step approach, one regression model is created using IPD from all available studies where patients remain clustered within each study(16). In the two-step approach, the IPD from each available study is analyzed separately in separate regression models, and then combined using traditional meta-analysis techniques(16). To achieve optimal flexibility and power for the IPD meta-analysis of prognostic factors, we used a one step approach rather than two-step approach to adjust for multiple covariates simultaneously across all studies, and to evaluate differences among patients within the same study and between studies (9, 13,16). Specifically, the one-step approach is suitable for controlling confounding by patient- and study- level covariates, increasing power to detect subgroup differences and interactions between prognosis in VA-ECMO patients and the selected covariates(17). The one-step approach is also useful when pooling data from non-randomized trials, and when studies have a small number of participants, as was anticipated here(17,18). There are fewer concerns about overfitting of the dataset than if a two-step approach was used, particularly when there are small sample of studies(17).

To assess prognostic factors for in-hospital and 1-year mortality, one-stage models with single covariate interactions were created with the following covariates selected *a priori* based on clinical importance(19–21):: recipient age, recipient sex, donor age, donor drug use, recipient donor undersizing by weight and predicted heart mass, pre-HT need for temporary MCS, prior sternotomy, and ischemic time. To avoid overfitting in multivariable analyses where each study centre had to be considered as a covariate, one-stage models with the following clinically selected covariates were conducted: recipient age, prior sternotomy, ischemic time. Age is a recognized risk factor for poor survival in patients receiving extracorporeal membrane support (21,22). Prior sternotomy was selected because it accounts for patients who have received previous cardiac surgery, including complex congenital patients and patients with previous durable ventricular assist devices, which may in turn reflect greater surgical risk at the time of HT, such as more complicated re-entry and greater need for blood products. Ischemic time is a risk factor for PGD and when prolonged, can impact graft quality and possibly the likelihood of recovery of graft function (3,23).

Pooled estimates for in-hospital and 1-year mortality were generated separately within each study and combined across studies using random effect models with STATA's mixed effects logistic regression model (xtmelogit) to provide odds ratios. xtmelogit is a STATA command based on logistic regression modeling that considers clustering of patients within studies(11).

Management of missing data

We imputed missing data if less than 20% of values were not available for any given variable. If more than 20% of values were missing for any given variable, the variable was

excluded from the analysis. We used multiple imputation by chained equations using Rubin's rule(24).

Assessment of the certainty of the evidence

We used the GRADE approach specific to prognostic factors to assess the certainty in the evidence between the prognostic factors examined and our outcomes of interest(25). We took a noncontextualized approach to assess the following domains: risk of bias, inconsistency, imprecision, indirectness and publication bias. We rated down for risk of bias for all prognostic factors that were not included in the adjusted analyses. The confidence in estimates for interventions and for prognostic factors was summarized as high, moderate, low, or very low.

PART IV: STATISTICAL ANALYSES, RISK OF BIAS AND GRADE FOR VA-ECMO RELATED INTERVENTIONS

The following section describes the methods used to evaluate the fourth study objective pertaining to the evaluation of the effect of different strategies while on VA-ECMO support on outcomes. The analysis addressed the relative impact of four different ways of delivering VA-ECMO interventions: peripheral vs. central cannulation; early cannulation after HT (defined as intraoperative cannulation) vs. late (defined as postoperative cannulation); use of LV unloading strategies (defined as use of IABP, Impella or surgical venting to unload the left ventricle) vs. no LV unloading strategies; and use of nitric oxide vs. no nitric oxide.

Assessment of risk of bias

Two reviewers (NA, TB) independently assessed the risk of bias for each of the included studies. Disagreements were resolved by consensus or through discussion with a third reviewer (AC). Risk of bias was assessed for effect of assignment to intervention (i.e., peripheral vs. central cannulation, early intraoperative vs. late postoperative cannulation) using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool for each outcome(26). Risk of bias was assessed for the following 7 domains: confounding, selection of study participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, reporting of results as defined by the ROBINS-I tool(26). Each domain and the overall risk of bias was assessed as "low", "moderate", "serious", or "critical". Adjudication of "no information" for each domain was avoided except for assessment of included studies presented only as conference abstracts.

Data synthesis and statistical analysis

We used RevMan Version 5.3(27) random effects models with the Mantel-Haenszel method to calculate pooled risk ratios for the effect of the following interventions on in-hospital mortality: central vs. peripheral cannulation, intraoperative vs. postoperative cannulation, LV unloading vs. no LV unloading, nitric oxide vs. no nitric oxide while on VA-ECMO support. 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.

Assessment of the certainty of the evidence

For study-level data, we used the GRADE approach to assess our confidence in the estimates from the gathered evidence and to present a summary of findings table(28). The confidence in estimates for interventions and for prognostic factors was summarized as high, moderate, low, or very low.

RESULTS

Description of search results

After removal of 496 duplicates, 2,638 studies underwent title and abstract screening, of which 119 studies were included in full text screening; of these 49 were suitable for study-level data meta-analysis (Figure 1). Of the 49 included studies, 15 studies provided IPD. Of the 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. Appendix 3.1 describes the reasons provided for non-availability of IPD by the 21 authors who responded but were not able to provide the data

Excluded studies

This analysis excludes 70 studies (Figure 1), of which 35 (50%) were duplicate or overlapping citations. 26 studies did not provide mortality data. Appendix 3.2 describes excluded studies for which additional consideration was given.

Description of included studies

All 49 included studies were observational cohort studies of HT recipients conducted between 1987 and 2018; 3 (6%) were prospective, 6 (12%) multicentre and 27 (55%) published as full texts. 23 (47%) were single cohort studies and 26 (53%) were comparative cohort studies. Of the 26 comparative/controlled cohort studies, 13 compared cohorts of VA-ECMO to no VA-ECMO or other temporary MCS, 7 compared different aetiologies of cardiogenic shock supported with VA-ECMO, 4 compared EGD to non-EGD cohorts, 1 study compared cohorts in different transplant eras, and 1 study compared adult to pediatric

patients who required VA-ECMO after HT. Studies providing IPD had more representation from non-North American centres and a more contemporary recruitment timeframe from 1997 to 2018 (Table 1).

Study-level data from the 49 included studies identified 1,477 patients who required VA-ECMO. Table 2 describes the baseline characteristics for all studies, as well as IPD and non-IPD studies separately. Table 3 describes the CHARMS-PF checklist of key items extracted from all included studies. The mean age of patients was 50 years, 23% were female, and the most common transplant indications were ischemic and non-ischemic cardiomyopathy. The cause of graft dysfunction was mostly primary graft dysfunction as per the ISHLT definition (85%), but less common causes of graft dysfunction requiring VA-ECMO were: pulmonary hypertension (10%), bleeding (1.7%), technical/surgical complication (0.5%), sepsis (0.5%) and hyperacute rejection (0.5%).

Individual patient data was provided for a total of 448 patients from 15 studies. Of 448 patients, 361 (81%) were successfully weaned from VA-ECMO support after a median of 5 days (IQR 3-8). Inotropic support was required for a median of 7 days (IQR 1-13). Length of stay in the ICU and in hospital were 14 days (IQR 8-23) and 34 days (IQR 16-70) respectively. VA-ECMO complications occurred in 240 (65%) patients: 101 (27%) experienced infection, 131 (35%) bleeding, 28 (7.5%) limb ischemia and 23 (6%) stroke. There were 76 (17%) patients with missing VA-ECMO complication outcomes. 314 (71%) patients survived 30 days, 273 (61%) survived to hospital discharge and 242 (54%) survived for 1 year after HT. There was no missing data for survival to 30 days or hospital discharge, but 3 (0.7%) patients had unknown vital status at 1 year. The most common causes of death

were: graft failure (25%), multi-organ failure (24%) and infection (20%). Follow up time for IPD patients was a median of 365 days (IQR 19 – 1,415). Follow up time for non-IPD was not routinely available, so no comparisons were made to the IPD length of follow up.

Risk of bias in included studies

Overall prognosis: Figure 2 presents the risk of bias for prognosis using QUIPS. Most (77%) studies adequately sampled the eligible population and were at low or acceptable risk of bias for the 'study participation' domain and short-term mortality outcome. The study attrition domain was judged low or acceptable risk of bias for nearly all (98%) studies since loss to follow up was uncommon for short-term mortality. The overall risk of bias was low or acceptable for 36 (77%) included studies that reported short-term mortality. The overall risk of bias was low or acceptable in 16 (73%) studies that reported 1-year mortality. There were no important issues identified in checking IPD. More than 20% data was missing for donor cause of death (21%), pre-transplant peripheral vascular disease (23%), sensitization (61%), recipient serum lactate (49%), induction immunosuppression (47%). Donor cause of death was an important missing variable because it was a prespecified prognostic factor of interest that we could not evaluate. There was less than 20% missing data for all remaining variables which were managed using multiple imputations. Data checking did not change the risk of bias within studies.

VA-ECMO complications: Figure 3 describes the risk of bias assessment using QUIPS for VA-ECMO complications of stroke, bleeding, limb ischemia, infection, and dialysis. Clear definitions for most outcomes were lacking; bleeding was poorly defined in 13 (68%) studies, infection in 17 (85%) studies, stroke in 15 (83%) studies, and limb ischemia in 14 (93%)

studies. Dialysis was likely measured reliably in 19 (95%) of studies. The overall risk of bias was high because of study confounding and inadequate control of other factors in this VA-ECMO population that may distort the association with these outcomes. NA and TB determined recipient age, pre-HT diabetes, pre-HT renal function, pre-HT peripheral vascular disease were important primary confounders for VA-ECMO complications.

VA-ECMO related interventions: We evaluated the risk of bias for the effect of VA-ECMO cannulation site, timing of ECMO, as well as the effect of LV unloading and nitric oxide using ROBINS-I (Table 4). The overall risk of bias for all studies was high because the ROBINS-I domain for confounding was assessed as high risk of bias. However, most of the studies included all eligible patients, defined the intervention, measured an objective outcome (i.e., mortality) and were consequently assessed as at low risk for these other domains.

Publication bias: The overall funnel plot for publication bias was visually symmetrical, however small study effects were present (Egger's p-value <0.01, Figure 4). A funnel plot of IPD and non-IPD studies appeared symmetrical on visual inspection, however the Eggers test p-value was <0.01 (Figure 4).

Estimates of prognosis

Short-term mortality: There were 47 studies that reported on short-term mortality, with a pooled estimate of 33% (95% CI: 28%, 39%, I^2=75%, Figure 5). There was substantial heterogeneity across the studies. Heterogeneity was not explained by subgroup analyses according to risk of bias (p=0.76), publication type (p=0.78), cause of EGD (i.e., PGD as per

the ISHLT definition, p=0.72), or recruitment timeframe (p=0.11, Figure 6). Meta-regression did not identify a significant relationship between short-term mortality and the following covariates: recipient age (p=0.78), sex (p=0.49), pre-transplant temporary MCS (p=0.09), ischemic time (p-0.93) and the use of any LV unloading strategy (p=0.95).

The overall estimate of 30-day mortality from the IPD studies was 31% (95% CI: 20%, 42%, I^2=82%) and in-hospital mortality of 43% (95% CI: 32%, 54%, I^2=80%, Figure 7). There was no significant difference in estimates of 30-day or in-hospital mortality between IPD and non-IPD studies (p=0.91 and p=0.17 respectively). We are moderately confident that the true prognosis for short-term mortality is likely to be close to the estimate, but there is a possibility that it might be different due to unexplained heterogeneity (Table 7).

One-year mortality: Twenty-six studies were pooled to provide an estimate of one-year mortality of 50% (95% CI: 43%, 57%, I^2=71%, Figure 8). There was substantial heterogeneity across the studies. Heterogeneity was not explained by subgroup analyses according to risk of bias (p=0.89), publication type (p=0.26), cause of EGD (p=0.82), or recruitment timeframe (p=0.23, Figure 9). 15 studies provided IPD with an overall estimate of 1-year mortality of 48% (95% CI: 39%, 57%, I^2=69%) with no significant difference in the estimate compared to non-IPD studies (interaction p=0.54, Figure 7). Overall, we are moderately confident that the true prognosis for 1-year mortality is likely to be close to the estimate, but there is a possibility that it is different due to unexplained heterogeneity (Table 7).

VA-ECMO related bleeding: 10 IPD and 13 non-IPD studies reported on the estimated risk of bleeding while supported on VA-ECMO. The pooled estimated risk of bleeding from the IPD studies was 37% (95% CI: 23%, 52%, Figure 10), and not different compared to the estimate from the non-IPD studies (39%, 95% CI: 24%, 54%) with an interaction p-value=0.87. We have moderate confidence that the true prognosis for bleeding while on VA-ECMO is likely to be close to the estimate, but there is a possibility that it is substantially different due to differences in the outcome definition between studies and lack of adjustment for confounding variables (Table 7).

VA-ECMO related infection: 11 IPD and 12 non-IPD studies reported on VA-ECMO related infection. The pooled estimated risk of infection from the IPD studies was 24% (95% CI: 17%, 31%, Figure 9) and not significantly different from the non-IPD studies' pooled estimate of 18% (95% CI: 7%, 31%, p=0.40, Figure 10). We are moderately confident that the true prognosis for VA-ECMO related infection is likely to be close to the estimate, but there is a possibility that it is substantially different due to differences in the outcome definition between studies and lack of adjustment for confounding variables (Table 7).

VA-ECMO related limb ischemia: 12 IPD and 8 non-IPD studies reported on limb ischemia. The pooled estimated risk of limb ischemia from the IPD studies was 6% (95% CI: 3%, 9%, Figure 10) and was not different from the non-IPD studies (4%, 95% CI: 0, 12%), interaction p=0.69. We are moderately confident that the true prognosis for VA-ECMO related limb ischemia is likely to be close to the estimate, but there is a possibility that it is substantially different due to differences in the outcome definition between studies and lack of adjustment for confounding variables (Table 7).

VA-ECMO related stroke: 12 IPD and 8 non-IPD studies reported on stroke. The pooled estimated risk of stroke from the IPD studies was 4% (95% CI: 2%, 7%, Figure 10) and was not different from the non-IPD studies pooled estimate (5%, 95% CI: 1%, 10%), interaction p=0.63. We are moderately confident that the true prognosis for stroke is likely to be close to the estimate, but there is a possibility that it is substantially different due to differences in the outcome definition between studies and study confounding (Table 7).

Dialysis: 14 IPD and 10 non-IPD studies reported on the risk of needing dialysis. The pooled estimated risk of dialysis from the IPD studies was 60% (95% CI: 49%, 69%, Figure 10) and was significantly greater than the pooled estimated risk of dialysis from non-IPD studies (29%, 95% CI: 16%, 44%), with interaction p=0.001. We have low confidence in the estimate because the true prognosis for dialysis may be substantially different from the estimate due to study confounding and significant differences in the estimate between IPD and non-IPD studies (Table 7).

Prognostic factors for mortality

Short-term mortality: Increasing recipient age (OR 1.02, 95%CI: 1.01-1.04; high certainty) was associated with in-hospital mortality (Table 5, 9). Prior sternotomy (OR 1.57, 95%CI :0.99-2.49; high certainty) and increasing donor age (OR 1.01, 95% CI 1.00-1.03; moderate certainty) probably increased in-hospital mortality (Table 5, 8). With moderate to high certainty, recipient sex, sex mismatch, ischemic time, pre-transplant LVAD are factors that may have little to no association with in-hospital mortality (Table 5, 8). There is low certainty in the effect estimates of the remaining prognostic factors.

One-year mortality: Factors associated with slightly higher 1-year mortality with high certainty include increasing recipient age (OR 1.02, 95% CI 1.00-1.04) and prior sternotomy (OR 1.56, 95% CI: 1.00-2.43). Increasing donor age probably increases 1-year mortality slightly (OR 1.01, 95% CI: 1.00-1.03; moderate certainty). Recipient sex, sex mismatch, ischemic time, pre-transplant LVAD may have little to no effect on 1-year mortality (Table 6, 10). Evidence regarding the remaining prognostic factors is low certainty with no clear association with 1-year mortality (Table 9).

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 that evaluated the effect of cannulation site on short-term mortality. Peripheral VA-ECMO cannulation may reduce in-hospital mortality compared to central VA-ECMO cannulation (RR 0.81, 95% CI: 0.60, 1.09, I^2=51%, Figure 11). The absolute effect of peripheral cannulation was 85 fewer deaths per 1,000, between 180 fewer to 40 more deaths. However, the confidence interval includes both benefit and harm in the use of peripheral cannulation with moderate heterogeneity between studies. Overall, there is very low certainty evidence that peripheral cannulation may reduce death by hospital discharge compared to central cannulation (Table 10).

Timing of cannulation: There were 11 IPD and 2 non-IPD studies that evaluated cannulation onto VA-ECMO early after HT (i.e., intraoperatively) vs. delayed (i.e., postoperatively). Pooling of data from all 13 studies of 399 patients showed a reduction in short-term death with early rather than delayed VA-ECMO cannulation (RR 0.76, 95% CI: 0.52, 1.09,

I^2=49%, Figure 11). The absolute effect of early cannulation was 115 fewer short-term deaths per 1000, ranging from 230 fewer deaths to 43 more deaths (Table 10). Due to confounding bias and few events, there is very low certainty evidence that early cannulation may reduce the risk of short-term death.

LV unloading: IPD from 10 studies was used to evaluate the effect of LV unloading strategies on in-hospital mortality. Pooling of data from 261 patients showed no benefit and possible harm in using LV unloading strategies in this population (RR 1.02, 95% CI: 0.77, 1.35, Figure 11). There was no heterogeneity between studies (I^2=0%). Due to confounding bias and very low event rates, there is low certainty evidence that LV unloading in VA-ECMO for EGD may result in little to no difference in the risk of short-term death (Table 10).

Use of nitric oxide: There were 5 IPD studies suitable to evaluate the effect of nitric oxide co-therapy in 80 patients supported on VA-ECMO on in-hospital mortality. Pooling of data from these 5 studies suggested no benefit and raised the possibility of harm when nitric oxide was used (RR 1.28, 95% CI: 0.86, 1.92, Figure 11). The heterogeneity between studies was likely not important for this outcome (I^2=6%). Overall, the evidence is very uncertain about the effect of nitric oxide on in-hospital mortality in patients supported with VA-ECMO for EGD (Table 10).

DISCUSSION

Main study findings

In this systematic review of 1,447 patients requiring VA-ECMO for EGD from 49 studies, we report an estimate of short-term mortality of 33% and 1-year mortality of 50%. VA-ECMO related bleeding and infection occurred in 38% and 21% of patients respectively, however rates of stroke and limb ischemia were low. Based on summaries of the evidence, we are moderately confident in our estimates; and we found no difference in estimates between studies that did and did not provide IPD. We identified recipient age and prior sternotomy as prognostic factors associated with in-hospital and 1-year mortality (high certainty evidence). Moreover, peripheral cannulation and early intraoperative cannulation may reduce in-hospital mortality compared to central cannulation and late postoperative cannulation, respectively (low certainty evidence).

Comparison to other studies

In comparison to other causes of cardiogenic shock that require VA-ECMO support, the use of VA-ECMO in our population is consistent with previous reports of higher rates of short-term survival (29). 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(8,29). In addition, we provide estimates of intermediate-term survival, which are not well reported for this population (30). 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 (30). Reasons for greater survival may be related to the younger age of transplant candidates in general, the higher likelihood of recovery of cardiac dysfunction, and lower rates of cardiopulmonary resuscitation at the time of ECMO cannulation(29,31).

Implications of prognostic factors on mortality

While several recipient, donor, and perioperative risk factors have been associated with developing graft dysfunction of any severity, less is known about factors that impact mortality in severe cases(23). In evaluating only patients with severe EGD requiring VA-ECMO with IPD, we identified recipient age, prior sternotomy and donor age as factors associated with mortality. We found that for every one-year increase in recipient age, 7 more people per 1000 died before hospital discharge in absolute terms. Older patient age is a common prognostic factor in both ECMO and PGD populations and has been incorporated into prediction scores such as the SAVE and RADIAL scores(31,32).

Prior sternotomy was a factor associated with lower survival to discharge and in absolute terms, associated with 96 more deaths per 1000 before hospital discharge. As a marker of any previous cardiac surgery including congenital surgery or durable MCS, previous sternotomy may reflect a more complicated re-operation, longer cardiopulmonary bypass times, and the need for more perioperative transfusions(33,34).

Lastly, donor age, which ranged from 14 to 63 years of age, may have a small impact on mortality. Older donor age has been implicated in a greater risk of PGD in general, and it is possible that an older graft has less cardiac reserve and lower ability to accommodate catecholamine shifts and may not tolerate the hemodynamic consequences of VA-ECMO support, such as LV loading.(20) Indeed, even though many HT patients are weaned from VA-ECMO, the impact of donor age reflects graft quality and likely contributes to the cause of death of graft failure in 25% of the study population.

Implications of VA-ECMO related complications

Bleeding and need for dialysis were common complications in our HT population and occurred at similar rates as in non-HT populations(35,36). While we have low certainty in the estimate of dialysis rates in this analysis, there is also heterogeneity and differences in reported rates of dialysis in the literature and it may reflect differences in patient or centre characteristics when it comes to the complexity and risk of HT cases(35). Infection risk in the HT population was similar to reported risk in non-immunosuppressed populations(37). Similarly, estimates of stroke and limb ischemia in our study were comparable to reported rates of stroke and limb ischemia across heterogenous groups of VA-ECMO patients(38).

Implications of VA-ECMO related interventions

As rates of VA-ECMO use rise, there is growing interest in optimizing decision-making and management of patients supported on this form of temporary MCS. Central vs. peripheral cannulation is an important consideration in patients who may require VA-ECMO at the time of cardiopulmonary bypass, with advantages and disadvantages to both techniques. While central cannulation is practically easier since the cannulas for cardiopulmonary bypass can be easily used, it is not necessarily the more advantageous approach(36,39). In a registry analysis of post-cardiotomy shock patients, central cannulation was associated with lower survival(40). We found peripheral cannulation may reduce in-hospital mortality in HT patients, which may reflect lower rates of bleeding and infection than would be encountered with an open chest in an immunocompromised patient.

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, early introduction of temporary MCS may be associated with improved survival.(41,42) Our findings raise the possibility that early cannulation in the operating room is associated with fewer deaths in EGD after HT compared to delayed postoperative cannulation. As research in this area is limited, ongoing evaluation for timing of VA-ECMO cannulation is warranted.

Limitations

Our review process was broad and extensive to account for all eligible studies however, there are limitations. While we could not acquire IPD for all the identified studies, there was no difference in estimates of mortality between IPD and non-IPD studies and therefore 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, however baseline characteristics for patients in the IPD and non-IPD studies were similar. Our decision to include studies published as of 2009 may introduce selection bias however, limiting to more contemporary work reduces the chances of overestimating mortality and reflects current VA-ECMO practices. Egger's testing suggested small study effects and possible publication bias in our review. However, we limited our systematic search to publications of ≥ 5 patients, to exclude case series and studies from small volume centres because VA-ECMO centre volume has been associated with mortality(43). Moreover, our funnel plots were symmetrical on visual exploration and tests for publication bias such as Egger's, may be less useful in prognostic research where heterogeneity is often high(25).

Lastly, the development and validation of a model incorporating recipient, donor, and intra-operative factors to estimate short-term mortality in HT patients supported with VA-ECMO was described in our study protocol but is not included here and will be conducted in a future project. Our findings are also limited to HT patients already supported with VA-ECMO and therefore may not be directly applicable to patient selection for VA-ECMO support in the first place.

CONCLUSIONS

In this largest systematic review of prognosis in HT patients who require VA-ECMO early after transplantation for severe graft dysfunction, approximately one-third of patients do not survive to hospital discharge. Prior recipient sternotomy, as well as increasing donor and recipient age are factors that negatively impact survival and may inform decision-making at the time of organ evaluation and acceptance. Early intraoperative cannulation and peripheral cannulation are techniques that may improve survival, however further research is needed to improve the certainty in the evidence pertaining to VA-ECMO techniques in this unique population.

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Figure 1. PRISMA-IPD Flow Diagram

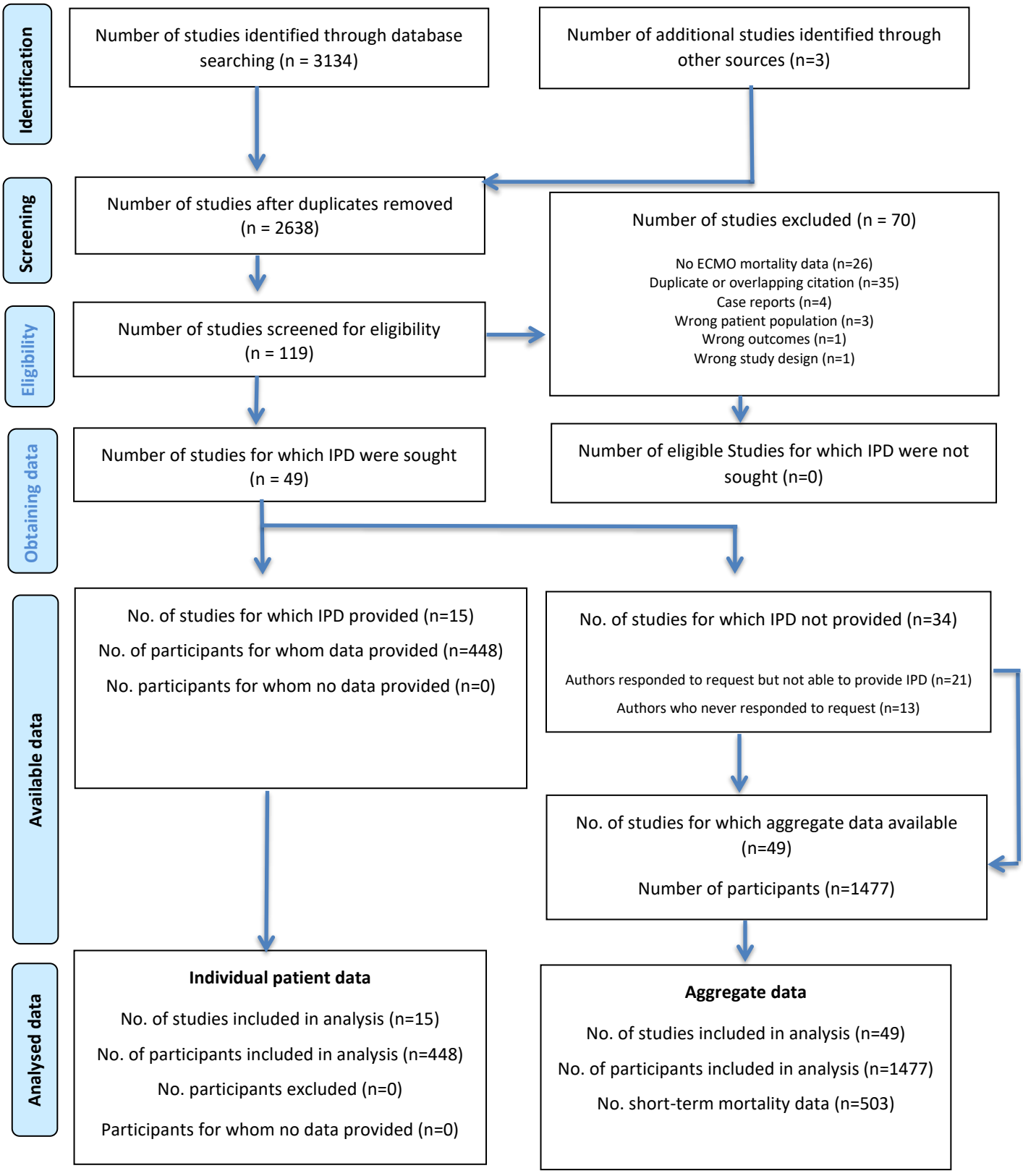


Figure 2. Modified QUIPS for overall prognosis in heart transplant recipients supported with VA-ECMO for early graft dysfunction

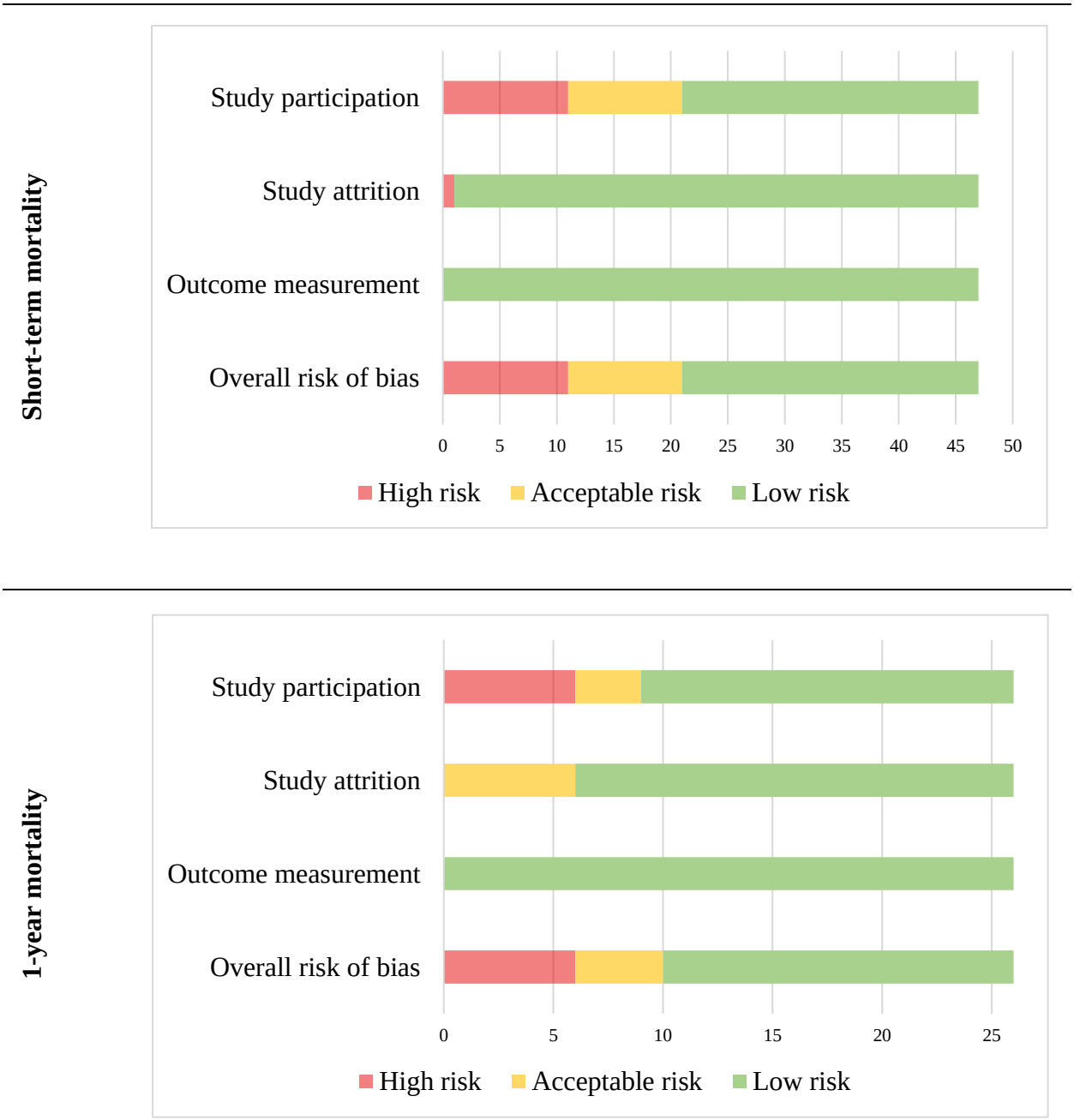


Figure 3. Modified QUIPS for VA-ECMO complications in heart transplant recipients supported with VA-ECMO for early graft dysfunction

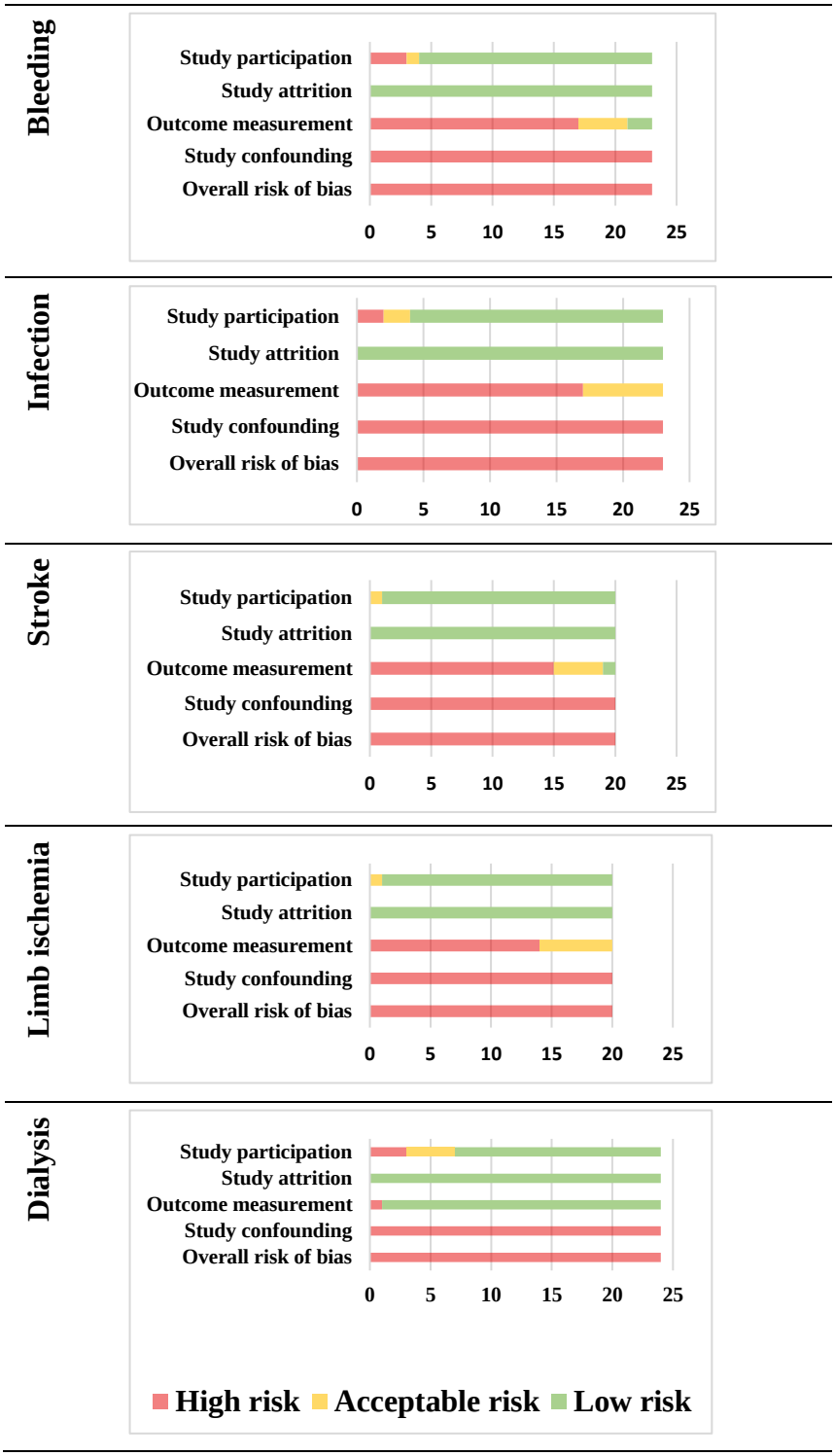
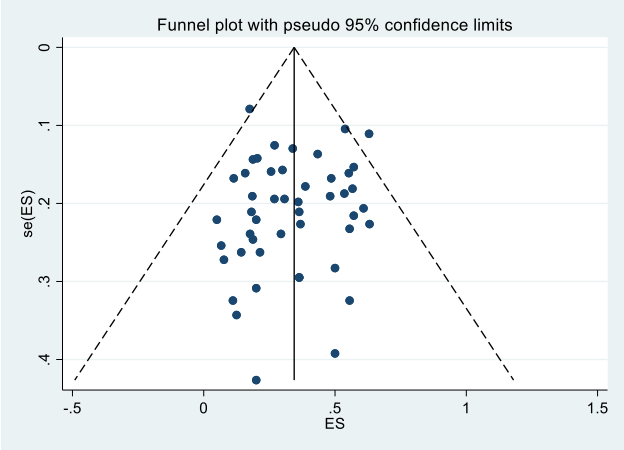


Figure 4. Funnel plot for publication bias for a) all included studies and b) for studies according to the provision of individual patient data

a)



b)

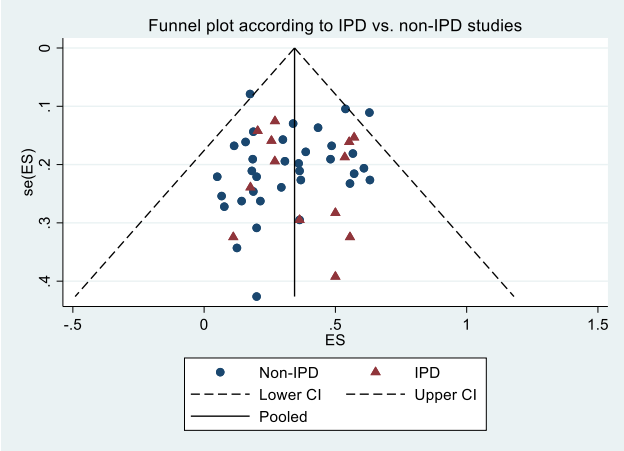


Figure 5. Forest plot of short-term mortality (30-day or in-hospital) expressed as a proportion.

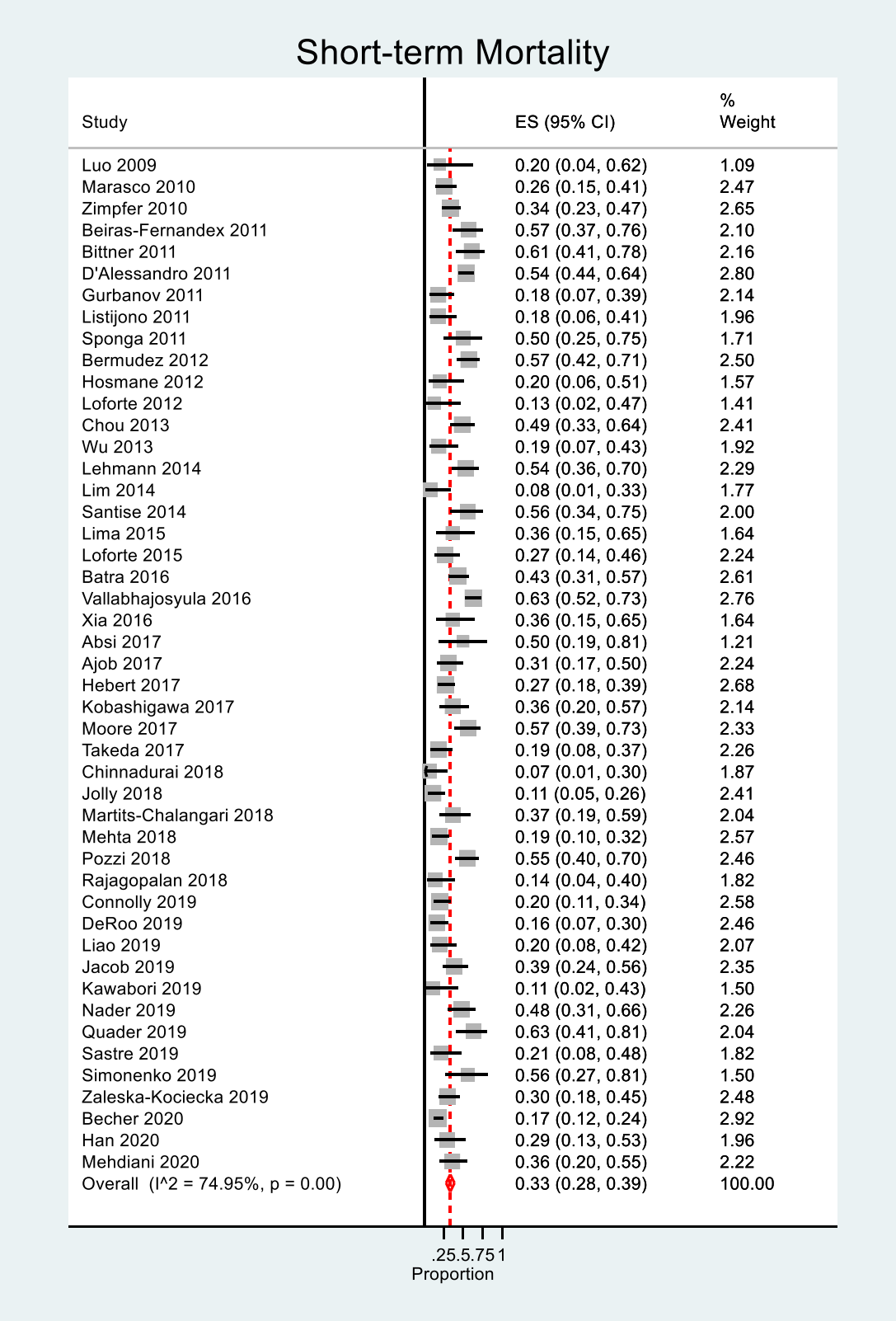
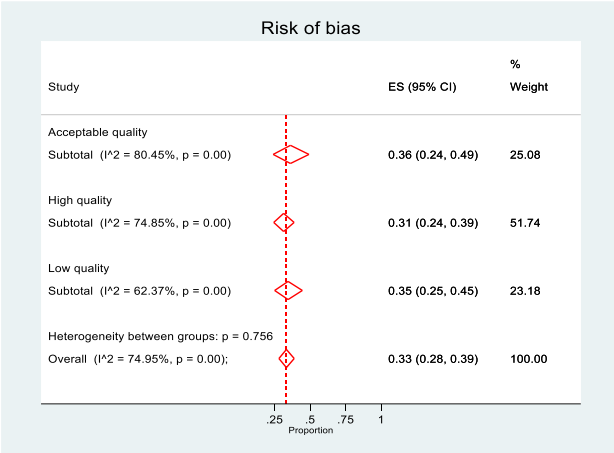
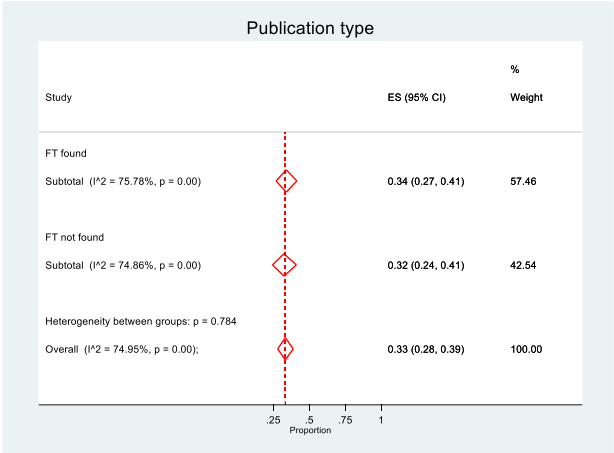


Figure 6. Forest plots of short-term mortality by subgroup analyses according to a) risk of bias, b) publication type, c) definition of early graft dysfunction, and d) recruitment timeframe.

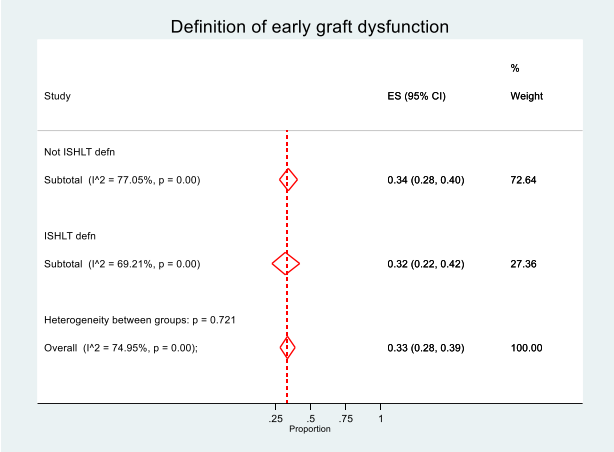
a)



b)



c)



d)

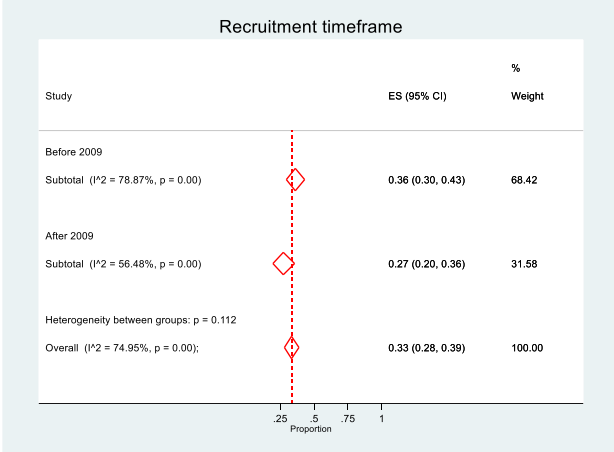
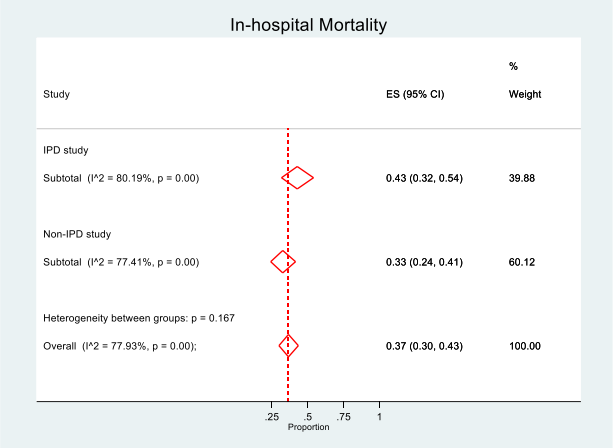


Figure 7. Forest plot according to studies that did and did not provide individual patient data for a) 30-day b) in-hospital and c) 1-year mortality

a)

b)



c)

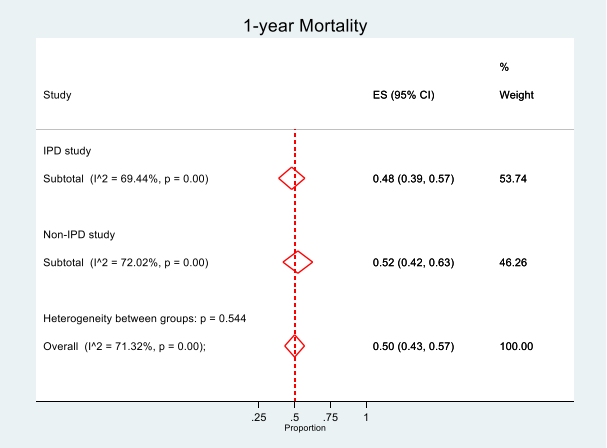


Figure 8. Forest plot of 1-year mortality expressed as a proportion.

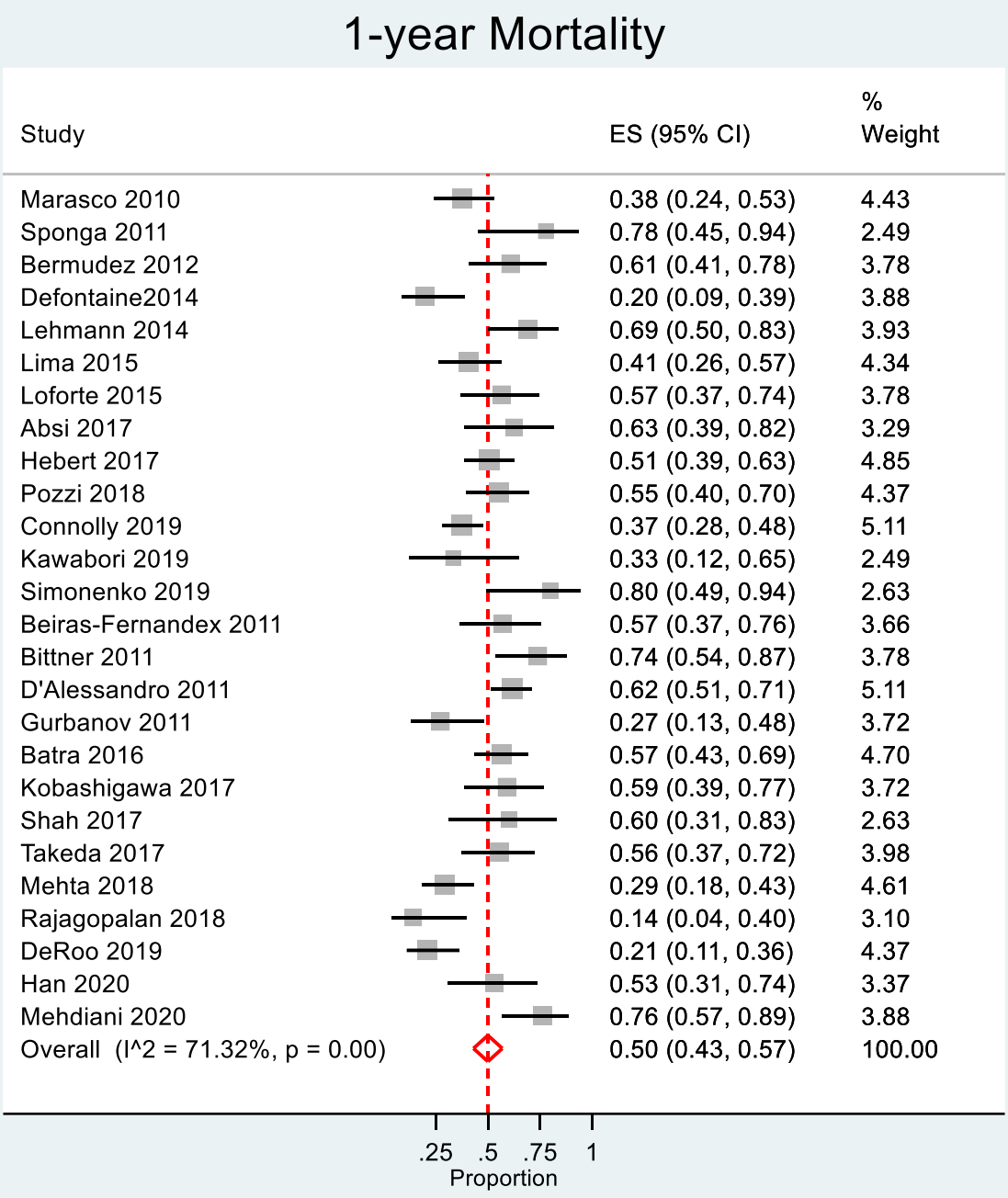
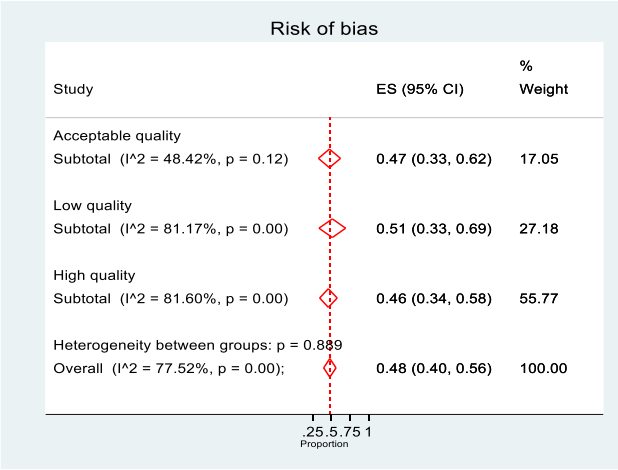
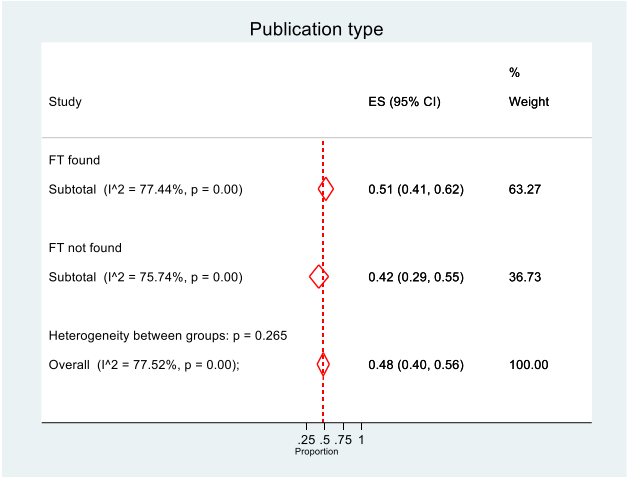


Figure 9. Forest plots of 1-year mortality by subgroup analyses according to a) risk of bias, b) publication type, c) definition of early graft dysfunction, and d) recruitment timeframe.

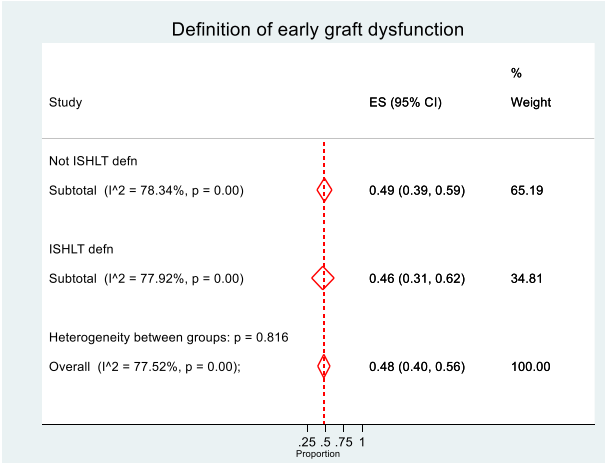
a)



b)



c)



d)

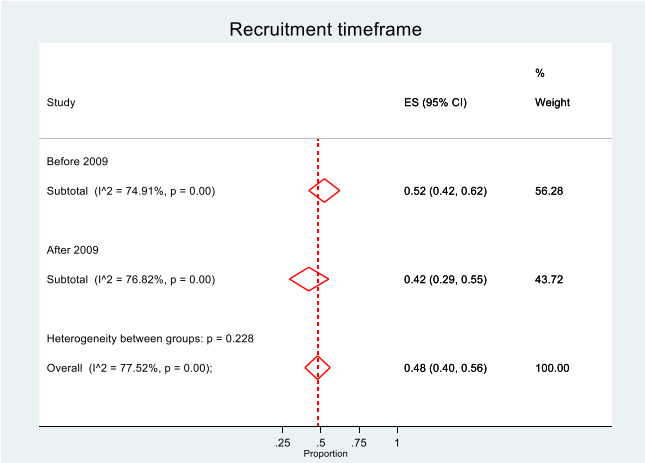
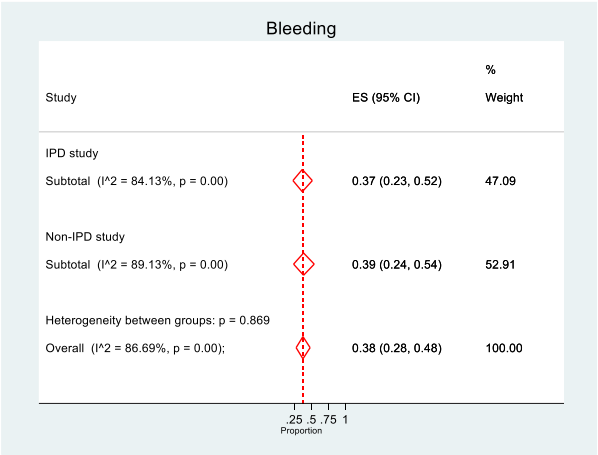
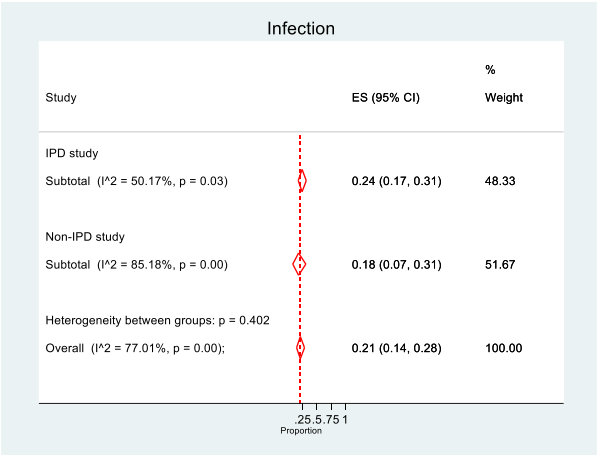


Figure 10. Forest plot of VA-ECMO complications according to studies that did and did not provide individual patient data for a) bleeding, b) infection, c) limb ischemia, d) stroke, and e) dialysis

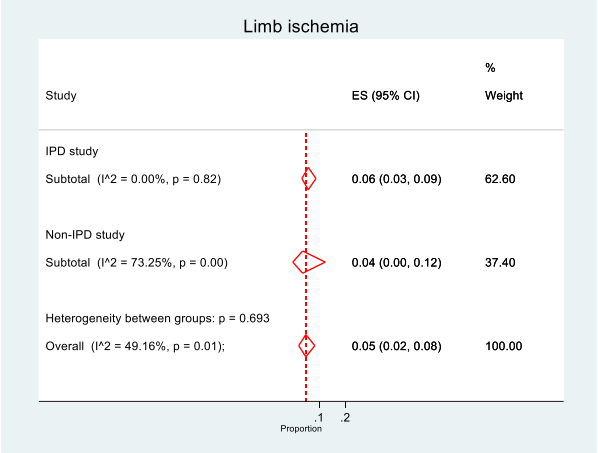
a)



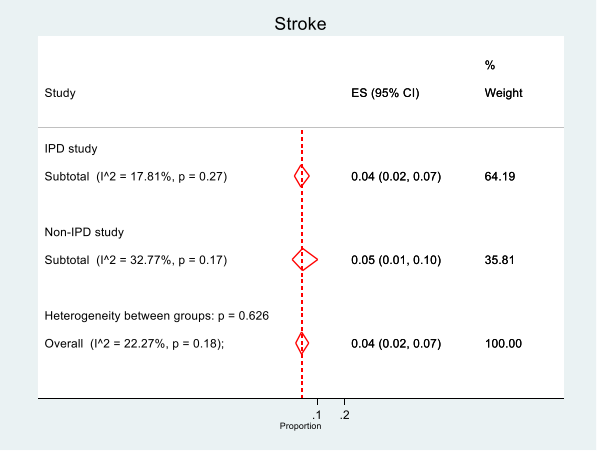
b)



c)



d)



e)

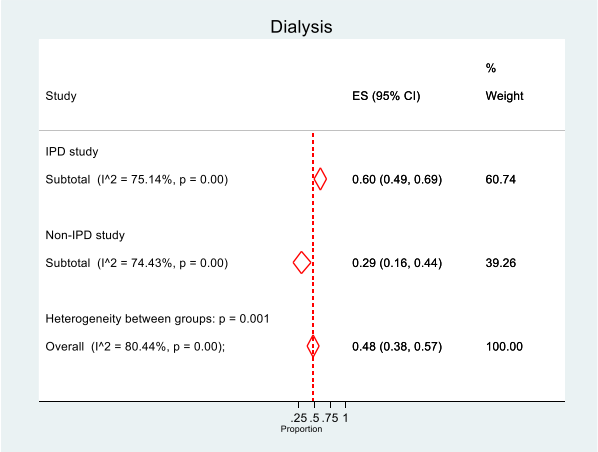
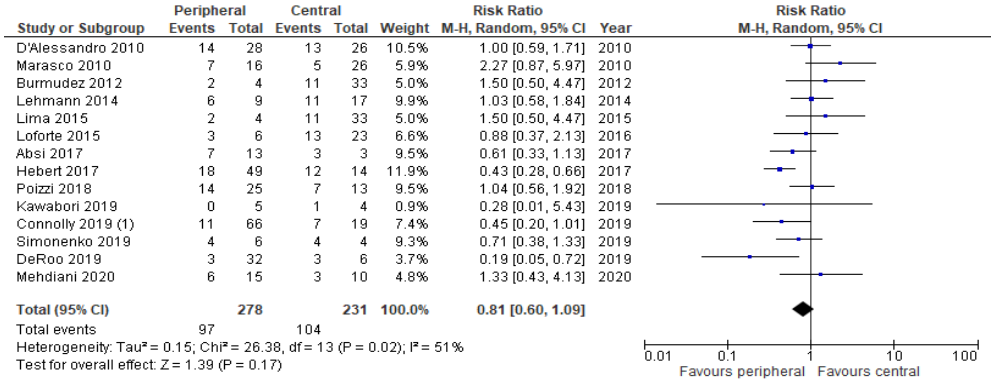


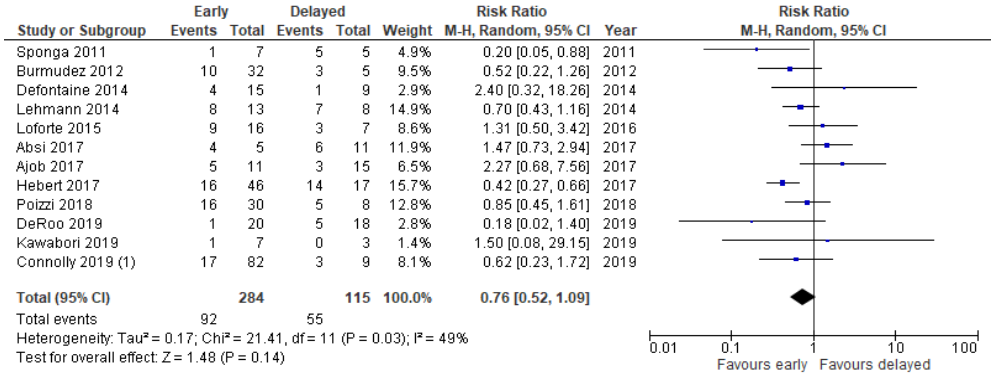
Figure 11. Forest plot of a) peripheral vs. central VA-ECMO cannulation, b) early intraoperative vs. delayed postoperative cannulation, c) left ventricular unloading vs. no loading while on VA-ECMO support, d) nitric oxide co-therapy vs. no nitric oxide while on VA-ECMO support on short-term mortality. Events refers to number of deaths.

a)



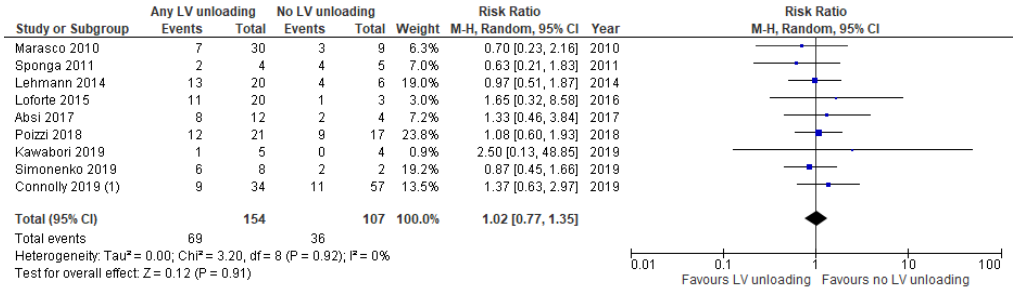
Footnotes
(1) Combined IPD from single centre published in Listijano 2011 and Connolly 2019

b)



Footnotes
(1) Combined IPD from single centre published in Listijano 2011 and Connolly 2019

c)



Footnotes
(1) Combined IPD from single centre published in Listijano 2011 and Connolly 2019

d)

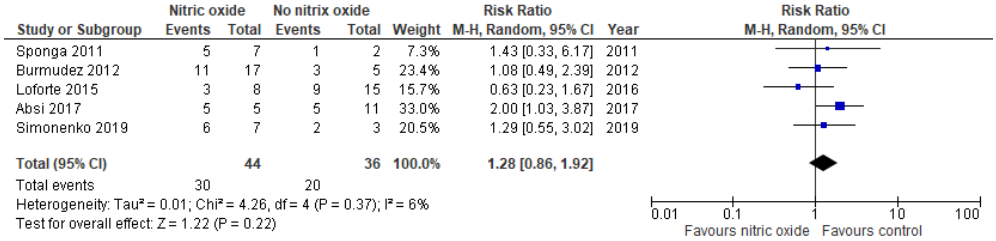

Nitric oxide
No nitrix oxide
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
Sponga 2011 5 7 1 2 7.3% 1.43 [0.33, 6.17] 2011
Burmudez 2012 11 17 3 5 23.4% 1.08 [0.49, 2.39] 2012
Loforte 2015 3 8 9 15 15.7% 0.63 [0.23, 1.67] 2016
Absi 2017 5 5 5 11 33.0% 2.00 [1.03, 3.87] 2017
Simonenko 2019 6 7 2 3 20.5% 1.29 [0.55, 3.02] 2019
Total (95% CI) 44 36 100.0% 1.28 [0.86, 1.92]
Total events 30 20
Heterogeneity: Tau² = 0.01; Chi² = 4.26, df = 4 (P = 0.37); I² = 6%
Test for overall effect: Z = 1.22 (P = 0.22)
0.01
0.1
1
10
100
Favours nitric oxide
Favours control

Table 1. Characteristics of included studies

Characteristic	Studies included in systematic review (n = 49)	IPD studies (n=15)	Non-IPD studies (n=34)
Single centre	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)

Continuous variables are expressed as means with standard deviations, and categorical variables are expressed as counts with percentages.

Table 2. Characteristics of patients from included studies

Characteristic	Non-IPD studies (n=1065)	No. of non-IPD studies reporting characteristic (n=34)	IPD studies (n=448) *
Recipient age (years)	51±13	17	50±13
Female	20	14	24
Dilated cardiomyopathy	42	9	34
Ischemic cardiomyopathy	42	11	36
Previous sternotomy	51	9	50
Pre-transplant VA-ECMO	28	4	10
Pre-transplant left ventricular assist device	39	10	28
Pre-transplant serum creatinine	133±43	8	126±72
Donor age (years)	37±11	12	38±13
Donor female	NR	NR	33
Cerebrovascular accident	38	1	40
Trauma	38	2	36
Anoxia	16	2	19
Ischemic time (minutes)	212±46	13	214±88
Cardiopulmonary bypass time (minutes)	240±54	7	219±113
Intra-operative ECMO	68	13	75
Post-operative ECMO	32	13	25
Central cannulation	28	13	44
Peripheral cannulation	72	13	56
IABP co-therapy	34	10	25
Nitric oxide co-therapy	8	3	79
Duration of ECMO support (days)	5.0±3.1	19	6.7±6.1 (Median 5.5, IQR 3-8)
Hospital length of stay (days)	32±30	19	51±56 (Median 32.5, IQR 15-65)

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.

Table 3. CHARMS-PF checklist of key items extracted (modified from Riley et al. BMJ 2019).

Study	Source of data	Participants						Outcomes				Sample size[2]			Missing data			Analysis[3]	Results[3]
	Cohort, registry data	**Consecutive**	**Number of centres**	**Setting, Location**	**Inclusion and exclusion criteria**	**Participant description, mean age % female**	**Study dates**	**Definition**	**Types of outcomes (single or combined endpoints)**	**Blinded outcome assessment**	**Time of outcome occurrence or duration of follow up**	**Number of participants**	**Number of short-term events**	**Number of events at 1 year**	**Number of participants with any missing value**	**Details of attrition**	**Handling of missing data**	**Modeling method**	**Prognostic effect estimates**
Luo 2009(44)	Cohort	NR	1	Fu Wai hospital, China	ECMO[1] for failure to wean off bypass on inotropes or IABP Exclusion NR	45 years 0%	2005 - 2008	Death on ECMO, death before discharge[4], re-HT	Single	No	By hospital discharge	5	1	NR	0	0 LTFU	Complete case analysis	No modeling	NA
Marasco 2010(5)	Cohort	Yes	1	The Alfred Hospital, Australia	Orthotopic and heterotopic HT Exclusion NR	49 23%	2000 - 2009	Death on ECMO, death before discharge, re-HT	Single	No	By hospital discharge	39	10	NR	0	0 LTFU	Complete case analysis	KM survival curves	ECMO vs. no ECMO after HT, p=0.007
Zimpfer 2010(45)	Cohort	Yes	1	Medical University Vienna, Austria	PGD after HT Exclusion NR	Age and sex NR	2000 - 2008	Death on ECMO, death before discharge and at 100 weeks	Single	No	100 weeks	59	20	NR	NR	NR	NR	KM survival curves	Early (2000-2003) vs. later experience (2004-2008), p=0.001 Timing of ECMO implantation, p=0.101
Beiras-Fernandex 2011(46)	Cohort	Yes	1	Grosshadern Clinic, Germany	ECMO post cardiotomy for failure to wean from bypass	49 Sex NR	1996 – 2006	Death at 30 days and 1 year	Single	No	1 year	21	12	12	NR	0 LTFU	Complete case analysis	No modeling	NA

					Exclusion NR													
Bittner 2011(47)	Cohort	NR	1	Heart Center Leipzig, Germany	Orthotopic HT with and without ECMO Exclusion NR	Age and sex NR	1997 – 2009	Death before discharge and 1 year, re-HT	Single	No	1 year	23	14	17	NR	0 LTFU	Complete case analysis	No modeling	NA
D'Alessandro 2011(48)	Cohort	Yes	1	Universite Pierre et Marie Curie, France	PGD that needed ECMO in first 48h post-op period Exclusion NR	47 20%	2003 – 2008	Death on ECMO, death before discharge and 1 year, re-HT	Single	No	1 year	91	49	56	0	0 LTFU	Complete case analysis	Multivariable logistic regression for RF for PGD KM survival curves	RF for PGD: age ≥60 (OR 2.11), pre-op MCS (OR 2.65), donor NE dose (OR 2.02), donor trauma as COD (OR 2.45), donor LVEF <55% (OR 2.72), ischemic time (OR 1.01) KM 5 year survival lower w/ PGF vs. no PGF (p<0.01)
Gurbanov 2011(49)	Cohort	NR	1	Anzhen hospital, China	Intraoperative and postoperative ECMO for HT Exclusion NR	48 23%	2005 – 2009	Death on ECMO, death at 30 days, before discharge and 1 year, re-HT	Single	No	1 year	22	4	6	0	0 LTFU	Complete case analysis	No modeling	NA
Listijono 2011(31)	Cohort	Yes	1	St. Vincent's Hospital, Australia	Adult HT patients Exclusion NR	49 Sex NR	2003 – 2008	Death on ECMO, death at 7 days, 30 days, before discharge and 6 months, re-HT	Single	No	6 months	17	3	NR	0	0 LTFU	Complete case analysis	No modeling	NA
Sponga 2011(51)	Cohort	NR	1	University Hospital of Udine, Italy	ECMO for PGD unresponsive to inotropes	39	2007 – 2010	Death on ECMO, death at 30 days, before	Single	No	1 year	12	6	7	0	0 LTFU	Complete case analysis	No modeling	NA

					Exclusion NR	42%		discharge and 1 year, re-HT										
Bermudez 2012(52)	Cohort	NR	1	University of Pittsburgh Medical Center, USA	Early graft dysfunction < 7 days Exclusion NR	Age and sex NR	2000 – 2011	Death at 30 days and 1 year	Single	No	1 year	42	24	28	NR	0 LTFU	Complete case analysis	Multivariable logistic regression for 30-day mortality	Preoperative cardiac surgery (HR:2.46,95%CI:1.13- 5.36,p=0.02), diabetes (HR:2.21,95%CI:0.99-5.01,p=0.05)
Hosmane 2012(53)	Cohort	NR	1	University Hospital of South Manchester, UK	Adult HT patients Exclusion NR	48 Sex NR	2006 – 2011	Death on ECMO, death at 30 days	Single	No	30 days	10	2	NR	NR	0 LTFU	Complete case analysis	No modeling	NA
Loforte **2012**(54)	Cohort	Yes	1	San Camillo Hospital, Italy	ECMO for cardiogenic shock Excluded patients with severe peripheral arterial disease, chronic renal failure, terminal malignancy, irreversible or severe degenerative brain disease, trauma, central ECMO	49 0%	2007 – 2011	Death on ECMO, death before discharge, re-HT	Single	No	By hospital discharge	8	1	NR	NR	0 LTFU	Complete case analysis	Multivariable logistic regression for 30-day mortality	Serum lactate at 72 h (OR 2.48), serum CK at 72h after ECMO initiation (OR 2.81), no. of PRBCs transfused on ECMO (OR 1.94)
Chou **2013**(55)	Cohort	Yes	1	National Taiwan University Hospital, Italy	ECMO anytime after HT Exclusion NR	36 Sex NR	1987 – 2010	Death before discharge	Single	No	By hospital discharge	35	17	NR	0	0 LTFU	Complete case analysis	KM survival curves	Lower survival at 5 years in PGD vs. non-PGD (p<0.01)
Wu **2013**(56)	Cohort	NR	1	NR, China	NR	Age and sex NR	2008 – 2011	Death on ECMO, death before discharge	Single	No	By hospital discharge	16	3	NR	NR	0 LTFU	NR	No modeling	NA

Defontaine 2014(57)	Cohort	Yes	1	Nantes, France	Adult HT patients Exclusion NR	Age and sex NR	2009 – 2012	Death at 1 year	Single	No	1 year	25	NR	6	0	0 LTFU	Complete case analysis	NR	NA
Lehmann 2014(58)	Cohort	NR	1	Heart Center Leipzig, Germany	VA ECMO after HT	46 18%	1997 – 2011	Death at 7 days, 30 days and 1 year	Single	No	1 year	28	15	21	NR	NR	NR	Multivariable logistic regression for mortality in all HTs	Low cardiac output (OR 11.3), stroke (0R=19.7)
Lim 2014(59)	Cohort	Yes	1	Seoul National University Hospital, Korea	Adult HT patients Exclusion NR	51 31%	2006 – 2012	Death on ECMO, death at 7 days, 30 days, before discharge, re-HT	Single	No	By hospital discharge	13	1	NR	0	0 LTFU	Complete case analysis	Multivariable logistic regression for risk for graft dysfunction requiring ECMO	Donor age (HR 0.986-1.120, p=0.125), preop MCS (HR 1.519-26.77, p=0.011), CPB (HR 1.001-1.019, p=0.033)
Santise 2014(4)	Cohort	Yes	1	Mediterranean Institute for Transplantation and Advanced Specialized therapies, Italy	Isolated HT with PGD requiring ECMO Exclusion NR	49 22%	2006 – 2013	Death on ECMO, death before discharge	Single	No	By hospital discharge	18	10	NR	NR	0 LTFU	Complete case analysis	No modeling	NA
Lima 2015(60)	Cohort	Yes	1	Int de Cardiol do Distrito Federal, Brazil	PGD within 24h after HT Excluded hyperacute rejection, pulmonary hypertension, surgical complications	34 36%	2007 - 2013	Death on ECMO, death at 7 days, 30 days, before discharge, re-HT	Single	No	By hospital discharge	11	4	NR	NR	0 LTFU	Complete case analysis	KM survival curves	
Loforte 2015(61)	Cohort	Yes	1	S. Orsola-Malpighi, Italy	ECMO for cardiogenic shock Excluded severe peripheral arterial disease, severe and chronic renal failure, terminal	46 62%	2004 – 2012	Death on ECMO, death before discharge and 1 year, re-HT	Single	No	1 year	26	7	11	NR	0 LTFU	Complete case analysis	Multivariable logistic regression for 30-day mortality	Lactate at 72h (OR 2.48, p=0.011), CK at 72h after ECMO initiation (OR 2.81, p=0.012)

					malignancy, irreversible and severe degenerative brain diseases, trauma														
Batra 2016(62)	Registry database	Yes	NR	New York, USA	Adults on ECMO after HT during index hospitalization Excluded non-New York state residents	NR	2003 – 2014	Death at 30 days, 90 days and 1 year	Single	No	1 year	53	23	30	NR	NR	NR	Multivariable logistic regression for 30-day mortality	Age > 65 (OR=2.20), CAD (OR 1.45), CKD (OR 1.5), liver disease (OR 1.42), CPR before ECMO placement (OR 2.62),yr of ECMO procedure, low volume center
Vallabhajosyula 2016(63)	Registry database	NR	NR	Pennsylvania, USA	ECMO after HT Excluded ECMO prior to HT	52 33%	2004 – 2014	Death before discharge	Single	No	By hospital discharge	81	51	NR	NR	0 LTFU	NR	Multivariable logistic regression for in-hospital mortality	Renal failure (OR 1.71), p=0.03
Xia 2016(64)	Cohort	Yes	1	Montefiore hospital, USA	All patients on ECMO for PGD Exclusion NR	54 Sex NR	2011 - 2015	Death on ECMO, death before discharge	Single	No	By hospital discharge	11	4	NR	0	0 LTFU	Complete case analysis	No modeling	NA
Absi 2017(65)	Cohort	NR	1	Hospital Universitario Fundacion Favaloro, Argentina	Adult orthotopic HT patients Exclusion NR	49 32%	2012 – 2016	Death on ECMO	Single	No	By hospital discharge	NA	3	NR	0	0 LTFU	Complete case analysis	NR	NA
Ajob 2017(66)	Cohort	NR	1	Strasbourg, France	PGD requiring ECMO Exclusion NR	Age and sex NR	2008 – 2015	Death at 30 days	Single	No	1 month	26	8	NR	NR	0 LTFU	Complete case analysis	NA	NR
Hebert 2017(67)	Cohort	Yes	2	Montreal Heart Institute, Canada	PGD requiring ECMO	48	2003 – 2013	Death at discharge and 1 year	Single	No	1 year	63	17	21	NR	0 LTFU	Complete case analysis	KM survival curves	1 year survival 79% early vs.

				Rennes, France	Exclusion NR	16%												16% late group, p=0.006
Kobashigawa 2017(68)	Cohort	NR	1	Cedars Sinai hospital, USA	ECMO within 48h after HT Exclusion NR	Age and sex NR	2010 – 2015	Death at 7 days, 30 days, before discharge, 6 month and 1 year	Single	No	1 year	22	8	13	NR	0 LTFU	Complete case analysis	No modeling	NA
Moore 2017(69)	Cohort	Yes	1	University of Nebraska Medical Center, USA	ECMO before and after HT Exclusion NR	62 Sex NR	2006 – 2017	Death at 30 days	Single	No	715 days	30	17	NR	NR	0 LTFU	Complete case analysis	No modeling	NA
Shah 2017(70)	Cohort	NR	1	UCLA, USA	All HT patients Exclusion NR	NR	2013 - 2015	Death at 1 year	Single	No	1 year	10	NR	6	NR	NR	NR	KM Survival curves	Survival at 1y ECMO 36% vs. 92% in no ECMO (p<.001)
Takeda 2017(6)	Cohort	Yes	1	Columbia University, USA	PGD supported with ECMO or CMAG pVAD within 24h of HT Exclusion NR	56 11%	2007 - 2015	Death on ECMO, death at 30 days, discharge and 1 year, re-HT	Single	No	1 year	27	5	15	0	0 LTFU	Complete case analysis	KM Survival curves	Survival at 3y (41% VAD vs. 66% VA-ECMO, p=0.13)
Chinnadurai 2018(71)	Cohort	Yes	1	Montefiore hospital, USA	All adult HT patients Excluded congenital patients, multi-organ transplants, donor heart ejection fraction <50% at time of HT or 40-55% initially	Age and sex NR	2014 – 2017	Death on ECMO, death before discharge	Single	No	By hospital discharge	15	1	NR	NR	0 LTFU	Complete case analysis	No modeling	NA
Jolly 2018(72)	Cohort	NR	1	Westchester Medical Center, USA	All adult HT patients	Age and sex NR	2013 – 2017	Death before discharge	Single	No	By hospital discharge	35	4	NR	NR	NR	NR	Regression for risk of ECMO for PGD	Donor death from drug OD (p <0.001), donor acidosis (p<0.001)

					Exclusion NR													
Martits-Chalangari 2018(73)	Cohort	Yes	1	Baylor University, USA	Severe PGD as per ISHLT definition Exclusion NR	58 16%	2012 – 2016	Death on ECMO, death at 30 days, re-HT	Single	No	By hospital discharge	19	7	NR	NR	0 LTFU	Complete case analysis	Multivariable logistic regression for risk of severe PGD	Donor undersized ≥ 30% by PHM (OR 6.86, 2.28-20.63), creatinine ≥ 2.0 mg/dL (OR 6.52, 1.90-22.38)
Mehta 2018(74)	Cohort	NR	1	Manchester University, UK	All HT patients who developed PGD Excluded other reasons for ECMO use	Age and sex NR	2006 – 2017	Death at 30 days and 1 year	Single	No	1 year	48	9	14	NR	NR	NR	KM survival curves	30-day survival 80.4% ECMO and 98.3% non-ECMO (p<0.001), 1-year survival 70% ECMO vs. 97.1% non-ECMO (p<0.001)
Pozzi 2018(75)	Cohort	NR	1	Louis Pradel Cardiologic Hospital, France	Adults with PGD as per ISHLT definition Excluded age < 18, use of ECMO for pulmonary hypertension or after 24h after HT	51 21%	2010 – 2016	Death on ECMO, death before discharge and 1 year, re-HT	Single	No	1 year	38	21	22	0	0 LTFU	Complete case analysis	KM survival curves	No difference in survival between PGD-LV and PGD-RV groups
Rajagopalan 2018(76)	Cohort	NR	1	Gill Heart and Vascular Institute, University of Kentucky, USA	ECMO for PGD after HT Exclusion NR	52 14%	2012 - 2017	Death before discharge and 1 year	Single	No	1 year	14	2	2	NR	0 LTFU	Complete case analysis	No modeling	NA
Connolly 2019(77)	Cohort	Yes	1	St. Vincent's Hospital, Australia	ECMO for PGD after HT Exclusion NR	53 33%	2009 – 2016	Death on ECMO, death before discharge and 1 year	Single	No	1 year	49	10	14	0	0 LTFU	Complete case analysis	Multivariable logistic regression for 1-year survival	Male (OR 7.48, p=0.031), baseline Cr (OR 0.99, p=0.019), duration of ECMO (OR 0.65, p=0.034)

DeRoo 2019(78)	Cohort	Yes	1	Columbia University, USA	ECMO for PGD after HT Exclusion NR	56 13%	2011 – 2017	Death on ECMO, death at 30 days, before discharge and 1 year, re-HT	Single	No	1 year	38	6	8	0	0 LTFU	Complete case analysis	Univariable Cox regression	74.6% lower risk of mortality in prompt vs. conservative ECMO, (CI, 0.05- 1.26; p=094)
Liao 2019(79)	Cohort	Yes	1	People's hospital of Zhonghsan City, China	ECMO before and after HT Excluded age <18	Age and sex NR	2012 – 2018	Death before discharge	Single	No	By hospital discharge	20	4	NR	3	NR	NR	Multivariate logistic regression for mortality	CPR before ECMO (OR 49, p=0.033)
Jacob 2019(80)	Cohort	Yes	2	Baylor University Medical Center, Mayo Clinic in Jacksonville, USA	ECMO for PGD as per ISHLT definition after HT Excluded non-ECMO mechanical circulatory support	57 16%	2005 - 2015	Death on ECMO, death at, 30 days and before discharge, re-HT	Single	No	By hospital discharge	31	12	NR	0	0 LTFU	Complete case analysis	Multivariate logistic regression	NR
Kawabori 2019(81)	Cohort	Yes	1	Tufts University, USA	ECMO for PGD after HT Exclusion NR	55 0%	2014 – 2018	Death on ECMO, death at 7 days, 30 days, before discharge and 1 year, re-HT	Single	No	1 year	9	1	2	0	0 LTFU	Complete case analysis	No modeling	NA
Nader 2019(80)	Cohort	Yes	1	Quebec Heart and Lung Institute, Canada	Post-cardiotomy shock requiring ECMO Excluded ECMO used for respiratory support	49 Sex NR	2009 – 2018	Death before discharge and 3 years	Single	No	3 years	27	13	NR	NR	NR	NR	No modeling	NA
Quader 2019(81)	Registry database	Yes	2	University of Virginia, USA	Adults after first HT	Age and sex NR	2001 – 2016	Death before discharge	Single	No	By hospital discharge	19	12	NR	NR	NR	NR	No modeling	NA

					Excluded re-transplantation														
Sastre 2019(82)	Cohort	Yes	1	Hospital Universitari de Bellvitge, Intensive Care Medicine, Spain	Adults needing ECMO Exclusion NR	Age and sex NR	2014 – 2018	Death before discharge	Single	No	By hospital discharge	14	3	NR	NR	NR	NR	No modeling	NA
Simonenko 2019(83)	Cohort	Yes	1	Almazov National Medical Research Centre, Russia	All HT patients Exclusion NR	Age and sex NR	2010 – 2018	Death at 30 days	Single	No	1 month	9	5	NR	NR	NR	NR	No modeling	NA
Zaleska-Kociecka 2019(84)	Cohort	Yes	1	Harefield Hospital London, UK	PGD requiring mechanical circulatory support Exclusion NR	44 385	2013 – 2018	Death on ECMO, death at 30 days and 90 days	Single	No	90 days	40	12	NR	NR	0 LTFU	Complete case analysis	No modeling	NA
Becher 2020(85)	Registry database	Yes	NR	Germany	All adults on ECMO Excluded age <18, ECMO used for primary respiratory failure	Age and sex NR	2007 – 2015	Death at 30 days	Single	No	NR	160	28	NR	NR	NR	NR	Multivariate Cox proportional regression for 30-day survival on VA-ECMO	NA as not specific to transplant
Han 2020(86)	Cohort	Yes	1	Stanford University, USA	All HT patients Excluded multi-organ transplants	52 23%	2010 – 2019	Death at 30 days and 1 year	Single	No	1 year	17	5	9	NR	NR	NR	KM survival curves Multivariable regression	30-day survival no PGD vs. severe PGD (97.6% vs. 68.7%, p<0.001) and 1-year survival (92.4% vs. 50.0% p<0.001). 8.6-fold increased risk

																			of death with severe PGD adjusted for age
Mehdiani 2020(89)	Cohort	Yes	1	Heinrich-Heine-University Medical School Dusseldorf, Germany	ECMO for PGD after HT Exclusion NR	54 28%	2010 - 2017	Death at 30 days and 1 year, re-HT	Single	No	1 year	25	9	19	0	0 LTFU	Complete case analysis	KM survival curves	No difference in 1 year survival between peripheral and central cannulation

[1] The term "ECMO" refers to VA-ECMO (veno-arterial extracorporeal membrane oxygenation) throughout.
[2] Sample size calculation is not relevant.
[3] Modified for the purposes of the types of studies evaluated.

HT = heart transplantation, LTFU = lost to follow up, NR = not reported

Table 4: Risk of bias assessment using the ROBINS-I tool for the effect of VA-ECMO interventions: cannulation location, timing of cannulation, use of LV unloading and use of nitric oxide

Study	Outcome	Overall risk of bias	Confounding	Selection of participants	Classification of intervention	Deviation from intended intervention	Missing data	Measurement of outcome	Selection of the reported results
Peripheral vs. central cannulation									
Marasco 2010	In-hospital mortality								
D'Alessandro 2010*	In-hospital mortality								
Listijano 2011	In-hospital mortality								
Burmudez 2012	In-hospital mortality								
Lehmann 2014	In-hospital mortality								
Lima 2015	In-hospital mortality								
Loforte 2015	In-hospital mortality								
Absi 2017	In-hospital mortality								
Hebert 2017	In-hospital mortality								
Poizzi 2018	In-hospital mortality								
Kawabori 2019	In-hospital mortality								
Connolly 2019	In-hospital mortality								
Simonenko 2019	In-hospital mortality								
Mehdiani 2020	30-day mortality								

Early intraoperative vs. delayed postoperative VA-ECMO									
Listijano 2011	In-hospital mortality								
Sponga 2011	30-day mortality								
Burmudez 2012	In-hospital mortality								
Defontaine 2014	In-hospital mortality								
Lehmann 2014	In-hospital mortality								
Loforte 2015	In-hospital mortality								
Absi 2017	In-hospital mortality								
Ajob 2017	30-day mortality								
Hebert 2017	In-hospital mortality								
DeRoo 2019	In-hospital mortality								
Kawabori 2019	In-hospital mortality								
Connolly 2019	In-hospital mortality								
Use of LV unloading vs. no unloading while on VA-ECMO support									
Marasco 2010	In-hospital mortality								
Listijano 2011	In-hospital mortality								
Sponga 2011	In-hospital mortality								
Burmudez 2012	In-hospital mortality								

Lehmann 2014	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟠	🟢	🟢
Loforte 2015	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Absi 2017	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Poizzi 2018	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Kawabori 2019	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Simonenko 2019	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Connolly 2019	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Use of nitric oxide vs. no nitric oxide while on VA-ECMO support									
Sponga 2011	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Burmudez 2012	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Loforte 2015	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Absi 2017	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢
Simonenko 2019	In-hospital mortality	🟠	🟠	🟢	🟢	🟢	🟢	🟢	🟢

No information	Low	Moderate	Serious	Critical

Table 5. Univariable and multivariable analysis of in-hospital mortality

Prognostic factor	**Univariable analysis**		**Multivariable analysis**	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Recipient age	1.02 (1.00, 1.04)	0.01	1.02 (1.01, 1.04)	0.01
Recipient sex	1.06 (0.65, 1.72)	0.82	-	-
Donor age	1.01 (1.00, 1.03)	0.09	-	-
Female donor to male recipient	0.54 (0.30, 0.97)	0.04	-	-
Ischemic time	1.00 (0.99, 1.00)	0.85	1.00 (0.99, 1.00)	0.82
Donor-recipient weight ratio	1.92 (0.74, 4.98)	0.18	-	-
Donor-recipient PHM ratio	1.57 (0.53, 4.71)	0.43	-	-
Pre-transplant temporary MCS	1.13 (0.39, 3.35)	0.79	-	-
Pre-transplant LVAD	0.95 (0.65, 1.38)	0.73	-	-
Prior sternotomy	1.51 (0.96, 2.38)	0.08	1.57 (0.99, 2.49)	0.06
Pre-transplant dialysis	1.38 (0.65, 3.02)	0.45	-	-

Table 6. Univariable and multivariable analysis of 1-year mortality

Prognostic factor	**Univariable analysis**		**Multivariable analysis**	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Recipient age	1.02 (1.00, 1.04)	0.02	1.02 (1.00, 1.04)	0.02
Recipient sex	1.07 (0.67, 1.70)	0.79	-	-
Donor age	1.01 (1.00, 1.03)	0.07	-	-
Female donor to male recipient	0.76 (0.44, 1.31)	0.33	-	-
Ischemic time	1.00 (0.99, 1.00)	0.82	1.00 (0.99, 1.00)	0.86
Donor-recipient weight ratio	1.18 (0.48, 2.93)	0.72	-	-
Donor-recipient PHM ratio	0.85 (0.30, 2.43)	0.76	-	-
Pre-transplant temporary MCS	0.97 (0.32, 2.94)	0.86	-	-
Pre-transplant LVAD	1.13 (0.80, 1.59)	0.52	-	-
Prior sternotomy	1.54 (1.00, 2.38)	0.06	1.56 (1.00, 2.43)	0.06
Pre-transplant dialysis	1.30 (0.61, 2.85)	0.53	-	-

Table 7. Summary of findings for prognosis: mortality and VA-ECMO complications

№ of studies	Certainty assessment					Effect			Certainty	Importance
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
30-day mortality										
32	not serious	serious[a]	not serious	not serious	none[e]	294	1012	event rate 30 per 100 (24 to 37)	⊕⊕⊕◯ Moderate	CRITICAL
In-hospital mortality										
38	not serious	serious[a]	not serious	not serious	none	414	1054	event rate 37 per 100 (30 to 43)	⊕⊕⊕◯ Moderate	CRITICAL
1-year mortality										
26	not serious	serious[a]	not serious	not serious	none	402	821	event rate 50 per 100 (43 to 57)	⊕⊕⊕◯ Moderate	CRITICAL
VA-ECMO complication: bleeding										
23	serious[b]	not serious[d]	not serious	not serious	none	262	748	event rate 38 per 100 (28 to 48)	⊕⊕⊕◯ Moderate	IMPORTANT
VA-ECMO complication: infection										
23	serious[b]	not serious[d]	not serious	not serious	none	166	725	event rate 21 per 100 (14 to 28)	⊕⊕⊕◯ Moderate	IMPORTANT
VA-ECMO complication: stroke										
20	serious[b]	not serious	not serious	not serious	none	40	616	event rate 4 per 100 (2 to 7)	⊕⊕⊕◯ Moderate	IMPORTANT
VA-ECMO complication: limb ischemia										
20	serious[b]	not serious	not serious	not serious	none	39	624	event rate 5 per 100 (2 to 8)	⊕⊕⊕◯ Moderate	IMPORTANT
Need for dialysis										
24	serious[c]	serious[a]	not serious	not serious	none	300	625	event rate 48 per 100 (38 to 57)	⊕⊕◯◯ Low	IMPORTANT

Explanations

a. Substantial unexplained heterogeneity, b. Outcome not well defined, study confounding, c. Study confounding, d. Heterogeneity can be explained by differences in outcome definitions, which is accounted for in the risk of bias assessment, e. Publication bias judged not significant because of the unreliability of Egger's test for observational data of proportions and overall symmetrical appearance of the funnel plots

Table 8. Summary of findings for prognostic 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 1yr increase)	Odds ratio 1.02 (95% CI: 1.01, 1.04)	Difference: 7 more deaths per 1000 (2 to 10 more per 1000)	High	Increasing 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 due to serious imprecision	Recipient sex makes little to no difference on in-hospital mortality
Donor age (Per 1yr increase)	Odds ratio 1.01 (95% CI: 1.00, 1.03)	Difference: 2 more deaths per 1000 (0 to 7 more per 1000)	Moderate due to risk of bias	Increasing donor age probably increases in-hospital mortality slightly
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 to 186 fewer per 1000)	Low due 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 due 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 due 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
Pre-transplant 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 due to serious imprecision and inconsistency	Pre-transplant temporary MCS may have little to no effect on in-hospital mortality, but our certainty is limited
Pre-transplant 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 due to serious imprecision	Pre-transplant 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
Pre-transplant 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 due to serious imprecision and inconsistency	Pre-transplant dialysis may or may not affect in-hospital mortality but our certainty in the estimate is limited

Table 9. Summary of findings for prognostic factors associated with one-year mortality

Prognostic Factor	**Study results Based on 445 patients from 15 studies**	**Absolute effect estimates**	**Certainty in effect estimates (Quality of evidence)**	**Plain text summary**
Recipient age (Per 1yr increase)	Odds ratio 1.02 (95% CI: 1.00, 1.04)	Difference: 5 more deaths per 1000 (1 to 10 more per 1000)	High	Increasing recipient age slightly increases 1-year mortality
Recipient sex (Female vs. male)	Odds ratio 1.07 (95% CI: 0.67, 1.70)	Difference: 16 more deaths per 1000 (94 fewer to 123 more per 1000)	Moderate due to serious imprecision	Recipient sex makes little to no difference on 1-year mortality
Donor age (Per 1yr increase)	Odds ratio 1.01 (95% CI: 1.00, 1.03)	Difference: 2 more deaths per 1000 (0 fewer to 7 more per 1000)	Moderate due to risk of bias	Increasing donor age may increase 1-year mortality slightly
Female donor to male recipient (Yes vs. no)	Odds ratio 0.76 (95% CI: 0.44, 1.31)	Difference: 70 fewer deaths per 1000 (181 fewer to 65 more per 1000)	Low due to serious imprecision and risk of confounding bias	Sex mismatch has little to no effect on 1-year 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 more deaths per 1000 (2 to 0 fewer per 1000)	High	Ischemic time makes little to no difference on one-year mortality
Donor-recipient weight ratio	Odds ratio 1.18 (95% CI: 0.48, 2.93)	Difference: 41 more deaths per 1000 (164 fewer to 225 more per 1000)	Low due to serious imprecision and inconsistency	Donor-recipient weight ratio may have little to no effect on 1-year mortality but our certainty in the estimate is limited
Donor-recipient PHM ratio	Odds ratio 0.85 (95% CI: 0.30, 2.43)	Difference: 41 fewer deaths per 1000 (245 fewer to 193 more per 1000)	Low due to serious imprecision and inconsistency	Donor-recipient PHM ratio may have little to no effect on 1-year mortality
Pre-transplant temporary MCS (Yes vs. no)	Odds ratio 0.97 (95% CI: 0.32, 2.94)	Difference: 8 fewer deaths per 1000 (236 fewer to 226 more per 1000)	Low due to serious imprecision and inconsistency	Pre-transplant temporary MCS may have little to no effect on 1-year mortality but our certainty in the estimate is limited
Pre-transplant LVAD (Yes vs. no)	Odds ratio 1.13 (95% CI: 0.80, 1.59)	Difference: 31 more deaths per 1000 (54 fewer to 108 more per 1000)	Moderate due to serious imprecision	Pre-transplant LVAD makes little to no difference on 1-year mortality
Prior sternotomy (Yes vs. no)	Odds ratio 1.56 (95% CI: 1.00, 2.43)	Difference: 98 more deaths per 1000 (0 fewer to 193 more per 1000)	High	Prior sternotomy probably increases 1-year mortality
Pre-transplant dialysis (Yes vs. no)	Odds ratio 1.30 (95% CI: 0.61, 2.85)	Difference: 65 more deaths per 1000 (115 fewer to 221 more per 1000)	Low due to serious imprecision and inconsistency	Pre-transplant dialysis may or may not affect 1-year mortality but our certainty in the estimate is limited

Table 10: Summary of findings for the effect of VA-ECMO interventions on short-term mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention (specified below)**	**Intervention (specified below)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Short-term mortality (death by 30 days or hospital discharge)												
14	observational studies	serious[a]	not serious	not serious	serious[b]	none	**Peripheral cannulation** 97/278 (35%)	**Central cannulation** 104/231 (45%)	**RR 0.81** (0.60 to 1.09)	**85 fewer per 1,000** (from 180 fewer to 40 more)	⊕⊕◯◯ Low	IMPORTANT
13	observational studies	serious[a]	not serious	not serious	serious[b]	none	**Early intraoperative cannulation** 92/284 (32%)	**Delayed postoperative cannulation** 55/115 (47.8%)	**RR 0.76** (0.52 to 1.09)	**115 fewer per 1,000** (from 230 fewer to 43 more)	⊕⊕◯◯ Low	IMPORTANT
10	observational studies	serious[a]	not serious	not serious	serious[b]	none	**Any LV unloading** 69/154 (45%)	**No LV unloading** 36/107 (34%)	**RR 1.02** (0.77 to 1.35)	**7 more per 1,000** (from 77 fewer to 118 more)	⊕⊕◯◯ Low	IMPORTANT
5	observational studies	serious[a]	not serious	not serious	very serious[b]	none	**Nitric oxide** 30/44 (68%)	**No nitric oxide** 20/36 (56%)	**RR 1.28** (0.86 to 1.92)	**156 more per 1,000** (from 78 fewer to 511 more)	⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study confounding was assessed as high risk

b. Optimal information size is too low, i.e. too few events

Appendix 1.1 Database search strategies

Ovid MEDLINE(R) ALL <1946 to May 14, 2020>
Search history sorted by search number ascending

#	Searches	Results	Type
1	exp Heart Transplantation/	35263	Advanced
2	(heart? adj3 transplant*).mp.	44525	Advanced
3	(heart? adj2 graft*).mp.	1219	Advanced
4	(heart? adj2 allograft*).mp.	1559	Advanced
5	(heart? adj2 allotransplant*).mp.	72	Advanced
6	(heart? adj2 homotransplant*).mp.	26	Advanced
7	(heart? adj2 homograft*).mp.	58	Advanced
8	(cardiac adj2 transplant*).mp.	11195	Advanced
9	(cardiac adj2 graft*).mp.	1063	Advanced
10	(cardiac adj2 allograft*).mp.	5154	Advanced
11	(cardiac adj2 allotransplant*).mp.	89	Advanced
12	(cardiac adj2 homotransplant*).mp.	13	Advanced
13	(cardiac adj2 homograft*).mp.	52	Advanced
14	or/1-13	48690	Advanced
15	Extracorporeal Membrane Oxygenation/	10264	Advanced
16	ecmo.mp.	7558	Advanced
17	ecls.mp.	1294	Advanced
18	ecpr.mp.	321	Advanced
19	(extracorporeal adj2 life support*).mp.	2113	Advanced
20	(extra-corporeal adj2 life support*).mp.	57	Advanced
21	(extracorporeal adj3 oxygenat*).mp.	14523	Advanced
22	(extra-corporeal adj3 oxygenat*).mp.	367	Advanced
23	(extracorporeal adj2 carbon dioxide removal*).mp.	203	Advanced
24	(extra-corporeal adj2 carbon dioxide removal*).mp.	8	Advanced
25	(extracorporeal adj2 carbondioxide removal*).mp.	1	Advanced
26	(extra-corporeal adj2 carbondioxide removal*).mp.	0	Advanced
27	(extracorporeal adj2 cardiopulmonary resuscitation*).mp.	499	Advanced
28	(extracorporeal adj2 cardio-pulmonary resuscitation*).mp.	12	Advanced
29	(extra-corporeal adj2 cardiopulmonary resuscitation*).mp.	7	Advanced
30	(extra-corporeal adj2 cardio-pulmonary resuscitation*).mp.	0	Advanced
31	(extracorporeal adj2 CPR).mp.	74	Advanced
32	(extra-corporeal adj2 CPR).mp.	2	Advanced
33	(extrapulmonary adj3 oxygenat*).mp.	20	Advanced

34	(extra-pulmonary adj3 oxygenat*).mp.	1	Advanced
35	minimax.mp.	441	Advanced
36	rotaflow.mp.	70	Advanced
37	cardiohelp.mp.	20	Advanced
38	deltastream.mp.	42	Advanced
39	biomedicus.mp.	175	Advanced
40	or/15-39	17103	Advanced
41	14 and 40	1211	Advanced
42	animals/ not (animals/ and humans/)	4665307	Advanced
43	41 not 42	1201	Advanced
44	limit 43 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)")	529	Advanced
45	limit 43 to ("all adult (19 plus years)" or "all aged (65 and over)")	524	Advanced
46	43 not 44	672	Advanced
47	45 or 46	828	Advanced
48	limit 47 to yr="2009 -Current"	642	Advanced
49	remove duplicates from 48	637	Advanced

Embase <1974 to 2020 May 14>

Search history sorted by search number ascending

#	Searches	Results	Type
1	exp heart transplantation/	64923	Advanced
2	(heart? adj3 transplant*).mp.	71234	Advanced
3	(heart? adj2 graft*).mp.	16168	Advanced
4	(heart? adj2 allograft*).mp.	2191	Advanced
5	(heart? adj2 allotransplant*).mp.	89	Advanced
6	(heart? adj2 homotransplant*).mp.	10	Advanced
7	(heart? adj2 homograft*).mp.	58	Advanced
8	(cardiac adj2 transplant*).mp.	16646	Advanced
9	(cardiac adj2 graft*).mp.	5385	Advanced
10	(cardiac adj2 allograft*).mp.	8665	Advanced
11	(cardiac adj2 allotransplant*).mp.	95	Advanced
12	(cardiac adj2 homotransplant*).mp.	3	Advanced
13	(cardiac adj2 homograft*).mp.	45	Advanced
14	or/1-13	79223	Advanced
15	extracorporeal oxygenation/	23316	Advanced
16	ecmo.mp.	16214	Advanced

17	ecls.mp.	2252	Advanced
18	ecpr.mp.	796	Advanced
19	(extracorporeal adj2 life support*).mp.	3357	Advanced
20	(extra-corporeal adj2 life support*).mp.	157	Advanced
21	(extracorporeal adj3 oxygenat*).mp.	25854	Advanced
22	(extra-corporeal adj3 oxygenat*).mp.	984	Advanced
23	(extracorporeal adj2 carbon dioxide removal*).mp.	401	Advanced
24	(extra-corporeal adj2 carbon dioxide removal*).mp.	12	Advanced
25	(extracorporeal adj2 carbondioxide removal*).mp.	6	Advanced
26	(extra-corporeal adj2 carbondioxide removal*).mp.	0	Advanced
27	(extracorporeal adj2 cardiopulmonary resuscitation*).mp.	833	Advanced
28	(extracorporeal adj2 cardio-pulmonary resuscitation*).mp.	23	Advanced
29	(extra-corporeal adj2 cardiopulmonary resuscitation*).mp.	24	Advanced
30	(extra-corporeal adj2 cardio-pulmonary resuscitation*).mp.	1	Advanced
31	(extracorporeal adj2 CPR).mp.	130	Advanced
32	(extra-corporeal adj2 CPR).mp.	5	Advanced
33	(extrapulmonary adj3 oxygenat*).mp.	19	Advanced
34	(extra-pulmonary adj3 oxygenat*).mp.	0	Advanced
35	minimax.mp.	655	Advanced
36	rotaflow.mp.	425	Advanced
37	cardiohelp.mp.	232	Advanced
38	deltastream.mp.	136	Advanced
39	biomedicus.mp.	572	Advanced
40	or/15-39	33472	Advanced
41	14 and 40	3653	Advanced
42	(exp animals/ or exp animal experimentation/ or nonhuman/) not ((exp animals/ or exp animal experimentation/ or nonhuman/) and exp human/)	6469139	Advanced
43	41 not 42	3585	Advanced
44	limit 43 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)	1044	Advanced
45	limit 43 to (adult <18 to 64 years> or aged <65+ years>)	1644	Advanced
46	43 not 44	2541	Advanced
47	45 or 46	2831	Advanced
48	limit 47 to yr="2009 -Current"	2500	Advanced
49	remove duplicates from 48	2466	Advanced

Cochrane Database of Systematic Reviews <2005 to Present>

Search history sorted by search number ascending

#	Searches	Results	Type
1	(heart? adj3 transplant*).ti,ab,kw.	15	Advanced
2	(heart? adj2 graft*).ti,ab,kw.	0	Advanced
3	(heart? adj2 allograft*).ti,ab,kw.	0	Advanced
4	(heart? adj2 allotransplant*).ti,ab,kw.	0	Advanced
5	(heart? adj2 homotransplant*).ti,ab,kw.	0	Advanced
6	(heart? adj2 homograft*).ti,ab,kw.	0	Advanced
7	(cardiac adj2 transplant*).ti,ab,kw.	4	Advanced
8	(cardiac adj2 graft*).ti,ab,kw.	0	Advanced
9	(cardiac adj2 allograft*).ti,ab,kw.	0	Advanced
10	(cardiac adj2 allotransplant*).ti,ab,kw.	0	Advanced
11	(cardiac adj2 homotransplant*).ti,ab,kw.	0	Advanced
12	(cardiac adj2 homograft*).ti,ab,kw.	0	Advanced
13	or/1-12	17	Advanced
14	ecmo.ti,ab,kw.	10	Advanced
15	ecls.ti,ab,kw.	0	Advanced
16	ecpr.ti,ab,kw.	2	Advanced
17	(extracorporeal adj2 life support*).ti,ab,kw.	0	Advanced
18	(extra-corporeal adj2 life support*).ti,ab,kw.	0	Advanced
19	(extracorporeal adj3 oxygenat*).ti,ab,kw.	10	Advanced
20	(extra-corporeal adj3 oxygenat*).ti,ab,kw.	0	Advanced
21	(extracorporeal adj2 carbon dioxide removal*).ti,ab,kw.	0	Advanced
22	(extra-corporeal adj2 carbon dioxide removal*).ti,ab,kw.	0	Advanced
23	(extracorporeal adj2 carbondioxide removal*).ti,ab,kw.	0	Advanced
24	(extra-corporeal adj2 carbondioxide removal*).ti,ab,kw.	0	Advanced
25	(extracorporeal adj2 cardiopulmonary resuscitation*).ti,ab,kw.	1	Advanced
26	(extracorporeal adj2 cardio-pulmonary resuscitation*).ti,ab,kw.	0	Advanced
27	(extra-corporeal adj2 cardiopulmonary resuscitation*).ti,ab,kw.	0	Advanced
28	(extra-corporeal adj2 cardio-pulmonary resuscitation*).ti,ab,kw.	0	Advanced
29	(extracorporeal adj2 CPR).ti,ab,kw.	1	Advanced
30	(extra-corporeal adj2 CPR).ti,ab,kw.	0	Advanced
31	(extrapulmonary adj3 oxygenat*).ti,ab,kw.	0	Advanced
32	(extra-pulmonary adj3 oxygenat*).ti,ab,kw.	0	Advanced
33	minimax.ti,ab,kw.	0	Advanced
34	rotaflow.ti,ab,kw.	0	Advanced
35	cardiohelp.ti,ab,kw.	0	Advanced

36	deltastream.ti,ab,kw.	0	Advanced
37	biomedicus.ti,ab,kw.	0	Advanced
38	or/14-37	12	Advanced
39	13 and 38	0	Advanced

Cochrane Central Register of Controlled Trials <2014 to Present>
Search history sorted by search number ascending

#	Searches	Results	Type
1	exp Heart Transplantation/	655	Advanced
2	(heart? adj3 transplant*).mp.	2058	Advanced
3	(heart? adj2 graft*).mp.	923	Advanced
4	(heart? adj2 allograft*).mp.	57	Advanced
5	(heart? adj2 allotransplant*).mp.	0	Advanced
6	(heart? adj2 homotransplant*).mp.	0	Advanced
7	(heart? adj2 homograft*).mp.	1	Advanced
8	(cardiac adj2 transplant*).mp.	598	Advanced
9	(cardiac adj2 graft*).mp.	168	Advanced
10	(cardiac adj2 allograft*).mp.	220	Advanced
11	(cardiac adj2 allotransplant*).mp.	2	Advanced
12	(cardiac adj2 homotransplant*).mp.	0	Advanced
13	(cardiac adj2 homograft*).mp.	0	Advanced
14	or/1-13	2896	Advanced
15	Extracorporeal Membrane Oxygenation/	162	Advanced
16	ecmo.mp.	517	Advanced
17	ecls.mp.	52	Advanced
18	ecpr.mp.	17	Advanced
19	(extracorporeal adj2 life support*).mp.	65	Advanced
20	(extra-corporeal adj2 life support*).mp.	2	Advanced
21	(extracorporeal adj3 oxygenat*).mp.	744	Advanced
22	(extra-corporeal adj3 oxygenat*).mp.	43	Advanced
23	(extracorporeal adj2 carbon dioxide removal*).mp.	23	Advanced
24	(extra-corporeal adj2 carbon dioxide removal*).mp.	0	Advanced
25	(extracorporeal adj2 carbondioxide removal*).mp.	0	Advanced
26	(extra-corporeal adj2 carbondioxide removal*).mp.	0	Advanced
27	(extracorporeal adj2 cardiopulmonary resuscitation*).mp.	22	Advanced
28	(extracorporeal adj2 cardio-pulmonary resuscitation*).mp.	0	Advanced
29	(extra-corporeal adj2 cardiopulmonary resuscitation*).mp.	1	Advanced
30	(extra-corporeal adj2 cardio-pulmonary resuscitation*).mp.	0	Advanced

31	(extracorporeal adj2 CPR).mp.	3	Advanced
32	(extra-corporeal adj2 CPR).mp.	0	Advanced
33	(extrapulmonary adj3 oxygenat*).mp.	1	Advanced
34	(extra-pulmonary adj3 oxygenat*).mp.	1	Advanced
35	minimax.mp.	58	Advanced
36	rotaflow.mp.	4	Advanced
37	cardiohelp.mp.	1	Advanced
38	deltastream.mp.	3	Advanced
39	biomedicus.mp.	16	Advanced
40	or/15-39	1043	Advanced
41	14 and 40	42	Advanced
42	limit 41 to yr="2009 -Current"	39	Advanced

Appendix 1.2 Study Protocol

Extracorporeal membrane oxygenation for early graft dysfunction following heart transplantation: A systematic review and meta-analysis

Protocol version: May 15, 2020

Principal investigators: Natasha Aleksova MD[1], Phyllis Billia MD PhD[1], Vivek Rao MD PhD[1], Heather J. Ross MD MHSc[1], Gordon Guyatt MD MSc[2], Ana C Alba MD PhD[1]

Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada

Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

Short title: Mortality in VA-ECMO for early graft dysfunction

INTRODUCTION

Graft dysfunction refers to impaired function of the left ventricle (LV), right ventricle (RV) or both ventricles of the donor graft after heart transplantation (HT). Early graft dysfunction (EGD) is a major cause of mortality following HT, with reported rates varying from 8 to 20%, and accounting for nearly 2/3 of deaths in the first 30 days post-HT(1). EGD can present very early (e.g. intra-operatively) or late during the first few days of the post-operative period. Early after HT, graft dysfunction is classified as primary (referred to as primary graft dysfunction, PGD) or secondary to a specific etiology such as sepsis, hyperacute rejection or surgical complications(1). The pathophysiology of PGD remains unclear, but risk factors include donor factors, organ procurement factors such as ischemic time and injury related to reperfusion of the organ, and recipient factors such as the need for pre-HT mechanical ventilation(1). The definition of PGD was not standardized until a recent consensus conference of the International Society of Heart and Lung Transplantation (ISHLT) in 2014 (1), which defined PGD as any degree of graft dysfunction in the first 24 hours post-HT classifying it into three categories of LV dysfunction: mild, moderate, and severe. Severe PGD of the LV refers to the need for left or biventricular mechanical support including veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and/or other forms of short-term mechanical circulatory support (MCS)(1). Severe graft dysfunction equates to cardiogenic shock and inevitably results in death if treatment is not initiated quickly. Initial therapy consists of medications to increase cardiac output and blood pressure to ensure that vital organs are well-perfused (2). If initial medical therapy fails to maintain adequate cardiac output, rapid initiation of MCS should be undertaken (3,4). The success of MCS depends on adequate timing of initiation, pre-existing patient comorbidities and severity of peripheral organ hypoperfusion.

In recent years, one of the most widely used forms of MCS is VA-ECMO. VA-ECMO has many advantages over other MCS because it provides bi-ventricular support, which is especially important in

patients with bi-ventricular dysfunction as is often the case in EGD (5). Furthermore VA-ECMO provides respiratory support through the addition of an oxygenator to the circuit in patients with concomitant respiratory failure. VA-ECMO cannulation can be central via a sternotomy or peripheral via peripheral vessels, and it can occur intra-operatively or early during the post-operative period.

Early graft dysfunction may be a severe but reversible process, and VA-ECMO can be used as a bridge to recovery or less commonly re-HT. Due to the significant risks and cost associated with VA-ECMO, timely decision -making, refined patient selection and the availability of an experienced team may favourably impact outcomes after VA-ECMO implant.

Previous meta-analyses have evaluated mortality in patients supported with VA-ECMO such as post-cardiotomy shock or myocarditis, but to our knowledge there are no meta-analyses evaluating mortality exclusively in patients following HT supported with VA-ECMO. Conducting a meta-analysis on study-level data may offer some benefit over individual study reports but still finding high variation of results across studies with insufficient exploration of the different sources of heterogeneity. The performance of IPD meta-analysis will offer the unique opportunity to explore factors related to mortality in this exclusive population.

OBJECTIVES

In this systematic review and IPD meta-analysis, we propose to evaluate prognosis y in patients with EGD who require VA-ECMO. To capture all baseline and perioperative patient characteristics and outcomes after placement on VA-ECMO, we will contact study authors to provide us with de-identified data regarding the patients included in all eligible studies identified in the systematic review. In this study, we will specifically:

1- Evaluate short-term mortality defined as 30-day mortality and factors associated with it.
2- Evaluate long-term mortality defined as 1-year mortality and factors at hospital discharge from the index hospitalization for HT associated with it.
3- Study the risk of major complications associated with VA-ECMO in the HT population.
4- Evaluate whether co-adjuvant interventions (i.e., those that provide left ventricular unloading, use of nitric oxide, etc.) impact short-term mortality.
5- Develop and validate a model incorporating recipient, donor, and intra-operative factors to estimate short-term mortality in HT patients supported with VA-ECMO.

METHODS

Data sources and searches: A research librarian conducted a systematic search of electronic databases from inception until June 17, 2019, including Medline, EMBASE, Cochrane, Centre for Reviews and Dissemination, Health Technology Assessment and NHS Economic Evaluation databases using several related terms: ("cardiogenic shock") OR ("extracorporeal membrane oxygenation") OR ("cardiac arrest") AND ("mortality"). Additional studies were identified by searching bibliographic references of included publications and previously published meta-analyses.

Due to concerns regarding citations not captured in the broad initial search of ECMO and mortality, a second comprehensive search strategy was developed by an information technologist to identify studies on heart transplantation and extracorporeal membrane oxygenation. The initial search strategy was developed for Ovid MEDLINE using a combination of database-specific subject headings and text words. The search strategy was then customized for each database. Searches were executed on May 15, 2020 in the following databases: Ovid MEDLINE, Ovid Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Clinical Trials. Searches were limited to human adults and years 2009-current.

Study selection: Eligible studies include observational or randomized studies of adult (>18 years) HT recipients who receive VA-ECMO during the index hospitalization after HT. Eligible studies report on mortality at any timepoint and comprise of those that reported on HT recipient outcomes separately or only reported on HT recipient outcomes. There will be no restrictions on language or lack of access to full text if the abstract provided sufficient information to characterize the population and mortality. Only studies with 5 or more patients and published as of January 1, 2009 are included in this analysis to represent more contemporary VA-ECMO strategies and management of patients. We excluded studies on multi-organ transplant recipients or pediatric recipients and case reports of less than 5 patients.

Using a study eligibility form, individual independent reviewers selected citations by screening titles and abstracts. Any citations deemed eligible were then included for screening of full-text versions of all articles by two independent reviewers. In cases of disagreement, consensus will be reached through discussion and participation of a third reviewer. Agreement between reviewers will be assessed by Cohen's kappa coefficient.

Data collection and management

After all eligible studies are identified via the systematic review, we will contact and invite by email all corresponding authors to share de-identified IPD using a personal letter. We will send 3 reminders separated by a week to increase author participation. After receiving author acceptance to participate in the IPD meta-analysis, we will provide a data sharing agreement to allow for transfer of data to our centre. Authors at each participating centre should seek for research ethical approval according to their institution standards.

Data abstraction and management

Data collection at each institution will be performed using a structured form. Each center will collect data to describe the population and center, assess outcomes and identify factors associated with mortality. These will include recruitment time frame, average number of transplants and ECMO per annum during that time frame, patient age and sex, pre-transplant diabetes, peripheral vascular disease, need for dialysis, mechanical ventilation, prior heart transplant, prior sternotomy, prior left ventricular assist device, prior ECMO, pre-transplant serum creatinine, bilirubin, albumin panel reactive antibody, and peak lactate immediately prior to ECMO implant, timing of ECMO implant in relation to HT, number of deaths at different time points and follow up times (e.g. mortality during ECMO support, mortality at discharge, 1-year mortality, etc.). We will collect information on the use of co-interventions including their timing/initiation, duration of ECMO support and its complications, including need for dialysis, bleeding requiring re-operation, limb ischemia with compartment syndrome or requiring amputation,

embolic or hemorrhagic stroke, and infection, and the number of patients who required re-transplantation and/or ventricular assist device after ECMO. We will also abstract HT-related variables, including donor age, sex, height and weight, donor cause of death if known, donor smoking, donor hypertension, donor diabetes, donor drug use, donor down time at time of arrest if applicable, time between down time and procurement, donor LVEF, donor use of inotropes, ischemic time, use of desensitization therapies at the time of HT, use of induction immunosuppression, and graft function after ECMO decannulation.

Quality assessment

We will collect center information to assess quality at the study-level and at the outcome level (e.g., mortality at hospital discharge, etc.). Risk of bias assessment for observational studies will be based on a customized version of the QUIPS (Quality in Prognosis Studies) tool (6,7). Items to appraise study quality will include patient selection (consecutive or random patient selection), study attrition (complete follow up), missing data for prognostic factor measurement and outcome measurement (objective and unbiased assessment).

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (8) assessing confidence in estimates across studies will be used to appraise our confidence in the estimates from the gathered evidence. We will assess risk of bias at outcome level considering risk of bias at the study-level along with inconsistency, imprecision, indirectness, and publication bias. We will formally assess publication bias with funnel plots. We will summarize confidence in estimates as high, moderate, low, or very low.

Data synthesis and statistical analysis:

Study population characteristics will be described using median and inter-quartile range (IQR) for continuous variables or counts and frequencies for categorical variables. Cumulative incidence function will be used to describe mortality after VA-ECMO support initiation considering clustering within the

study. We will use mixed logistic regression models to evaluate the association between factors and outcomes including short- and long-term mortality and ECMO related complication considering study clustering by fitting studies as a random effect. We will select co-variates entered in the multivariable models based on clinical and top-ranked statistical significance avoiding model overfitting. The output of this model will be expressed as odds ratio and their respective 95% confidence interval.

We will develop and validate a model to estimate short-term mortality (at 30 days) in HT patients supported with VA-ECMO using mixed model logistic regression with study fitted as random effect. Depending on the number of participating centers, we will perform model validation by bootstrapping (low number of participating studies) or by external validation diving the sample into thirds, using two thirds for model derivation and the remaining third of the sample for model validation (if high number of participating studies with more than 200 events). We will evaluate model discrimination and calibration. We will assess discrimination using the area under the receiving operator curve (9). We will evaluate calibration by evaluating the relationship between observed and predicted survival by risk deciles using linear regression reporting the coefficient of determination (R^2) and illustrating using a scatter plot. A higher R^2 represents higher accuracy; a value of 1 means perfect accuracy. We will compare our model's performance to that of the published Survival After VA-ECMO (SAVE) score (10).

Lastly, we will evaluate the effect of co-interventions on short-term mortality using multivariable mixed logistic regression models. Adjusting co-variates will be selected as previously described. The co-interventions tested with be LV venting strategies (e.g. IABP, Impella, surgical venting, etc.), and use of nitric oxide.

Missing values in factors and covariates will be imputed using multiple imputations with 10 repetitions using the multivariate imputation chain equation (11,12). The results from each imputed dataset will be pooled as per Rubin's rules (13).

A two-sided p-value of 0.05 or lower was considered statistically significant. Stata 12 (Indonesia) will be used to perform data analysis and to generate graphs.

Data management and ethical considerations

The de-identified shared data will be stored on a secured and encrypted electronic database housed only on the TGH secure network and accessible only by the study investigators. Hard copies of any data will be stored in a secure locked cabinet at TGH. Study records will be maintained for the designated 10-year retention period in a secure fashion as described above. Once the mandatory retention period has passed, all electronic and hard-copy data will be disposed of according to UHN policy.

This is a systematic review and IPD meta-analysis on retrospectively collected data, which already exists and has been previously published as journal articles or abstracts. Thus, there will be no patient contact and patient consent will not be sought for this specific study. There is minimal risk to patients apart from a breach of confidentiality, and there are adequate provisions in place to protect against this. All study information will be de-identified, and results will be presented in aggregate manner.

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Appendix 1.3 Screening form with inclusion and exclusion criteria for study selection

Paper:		
• Any language, published as of January 1, 2009	**YES**	**NO**
• Non-randomized OR randomized trials	**YES**	**NO**
• Not case report, must be 5 or more subjects	**YES**	**NO**

Population:		
• Adults, age 18 and above	**YES**	**NO**
• De novo heart or re-transplantation	**YES**	**NO**
• Not multiple simultaneous organ transplants, e.g. heart-lung	**YES**	**NO**

Intervention:		
• VA-ECMO during the index hospitalization for heart transplantation	**YES**	**NO**

Comparison:		
• Any comparative group or no comparison	**YES**	**NO**

Outcomes reported:		
• Mortality at any time point after VA-ECMO implantation	**YES**	**NO**

Type of article:		
• Observational comparative (2 or more cohorts) or non-comparative (single cohort) studies • Randomized controlled trial • Meta-analysis (to identify studies)	**YES**	**NO**

Duplicated population:		
• If duplicated, does this study provide new information?	**YES**	**NO**
• If duplicated, is study more recent?	**YES**	**NO**

Study inclusion:	
• All the answers are YES	**INCLUDE**
• Any answer is NO	**EXCLUDE**

Appendix 2.1 Email template for contacting study authors to obtain individual patient data

Date_____

Dear Dr._____,

We are a group of researchers at Toronto General Hospital, Toronto, Canada conducting a patient-data level meta-analysis to characterize outcomes in adults who are placed on VA-ECMO for primary graft dysfunction following heart transplantation. We would like to include your study entitled:

"Title of study" published as a full text in the *Journal* _____.

We hope you would be able to provide us with de-identified data regarding the patients included in your study in terms of baseline and perioperative characteristics and outcomes after placement on VA ECMO.

If you find this project interesting, we would like to invite as a co-author and share with you the proposal and data collection form. Once you have reviewed this material, we can start the process for data transfer.

Thank you for taking the time to consider our request. We welcome the opportunity to work with you.

Sincerely,

Natasha Aleksova, MD
Research fellow
Advanced heart failure and transplantation
Peter Munk Cardiac Centre, Toronto General Hospital
Natasha.aleksova@uhn.ca

Heather Ross, MD, MSc
Cardiologist
Advanced heart failure and transplantation
Peter Munk Cardiac Centre, Toronto General Hospital
Heather.ross@uhn.ca

Carolina Alba, MD, PhD
Cardiologist
Advanced heart failure and transplantation
Peter Munk Cardiac Centre, Toronto General Hospital
Carolina.alba@uhn.ca

Appendix 2.2 Variables sought for individual patient data

Variable name	Manuscript label	Variable Description	Type	Coding legend	
Study ID	n/a	Anonymous coding for study	Nominal	n/a	
Study author	Corresponding author from eligible study			n/a	
Study center	Center where study conducted	City and hospital		n/a	
Study country	Country where study conducted			n/a	
Study timeframe	Lower and upper recruitment time (month/year)	Time during which patients were recruited into study	continuous	n/a	
ECMO/year	Number of ECMO implants per year	Number of **ALL** ECMO implants (PGD and non-PGD) at centre during study timeframe	continuous	n/a	
Transplant/year	Number of heart transplant at center per year	Number of heart transplant at center per year	continuous	n/a	
Donor Age	Donor Age (years)	Donor age at transplant	continuous	n/a	
Donor Sex	Donor sex	Donor sex	Binary	Male	1
				Female	2
Donor COD	Donor cause of death	Donor cause of death	Nominal	Unknown/Other	1
				Anoxia	2
				CNS Tumor	3
				CVA/ Stroke	4
				Head trauma or trauma	5
Donor down time	Donor down time at time of initial cardiac arrest (minutes)	Time between start of CPR and return of spontaneous circulation in the donor at time of cardiac arrest if applicable (minutes)	Continuous	n/a	
Donor height	Donor Height (cm)	Donor height	Continuous	n/a	
Donor weight	Donor Weight (kg)	Donor weight	Continuous	n/a	
Donor BMI	Donor BMI (Kg/m2)	Donor BMI (Kg/m2)	continuous	n/a	
Donor Diabetes	Donor diabetes	Donor diabetes	Nominal	unknown	0
				none	1
				Type 1	2
				Type 2	3
Donor Hypertension	Donor hypertension	Donor hypertension	Nominal	unknown	0
				no	1
				yes	2
Donor Smoking	Donor smoking	Donor smoking (ever smoker)	Nominal	unknown	0
				no	1
				yes	2

Donor Drug Use	Donor drug use	Donor drug use	Nominal	unknown	0
				no	1
				yes	2
Type of Donor Drug Use	Type of donor drug use	Type of donor drug used if known	Nominal	Cocaine	1
				Amphetamines	2
				Opioids	3
Donor inotropic support	Use of any inotropes in donor pre-transplant	Donor inotropes	Nominal	unknown	0
				no	1
				yes	2
Donor angiogram	Donor coronary angiogram performed	Donor coronary angiogram performed	Nominal	unknown	0
				no	1
				yes	2
Donor angiogram results	Findings of donor coronary angiogram	Findings of donor coronary angiogram	Continuous	n/a	
Donor LVEF	Left ventricular ejection fraction by echo	Donor left ventricular ejection fraction by echo	Continuous	n/a	
Recipient age	Recipient age (years)	Recipient age at transplant	Continuous	n/a	
Recipient sex	Recipient sex	Recipient sex	Binary	Male	0
				Female	1
Transplant date	Transplant date (day/month/year)	Date of the transplant	continuous	n/a	
Recipient weight	Recipient Weight (kg)	Recipient Weight	continuous	n/a	
Recipient BMI	Recipient BMI (Kg/m2)	Recipient BMI (Kg/m2)	continuous	n/a	
Cardiomyopathy	Primary Diagnosis	Heart Failure Etiology	Nominal	Other	1
				Ischemic	2
				Valvular	3
				Congenital	4
				Idiopathic dilated	5
				Hypertrophic	6
				Myocarditis	7
Pre-transplant DM	Pre-transplant diabetes mellitus	Diagnosis of diabetes mellitus prior to transplant	Nominal	no	1
				yes	2
Pre-transplant PVD	Pre-transplant peripheral vascular disease	Documented peripheral vascular disease prior to transplant	Nominal	no	1
				yes	2
Pre-transplant dialysis	Pre-transplant dialysis	Dialysis, any form, in 2 weeks prior to transplant	Nominal	no	1
				yes	2
Pre-transplant mechanical ventilation	Pre-transplant mechanical ventilation	Mechanical ventilation in 2 weeks prior to transplant	Nominal	no	1

				yes	2
Prior heart transplant	Previous heart transplantation	If recipient had a heart transplant prior to this event	Binary	No	1
				Yes	2
Prior sternotomy	Previous Sternotomy	If recipient had previous sternotomies	Binary	No	1
				Yes	2
Prior VAD	VAD	If recipient had a ventricular assist device in the preoperative period	Nominal	none	0
				LVAD	1
				RVAD	2
				BiVAD	3
Prior ECMO	ECMO	If recipient had ECMO in the preoperative period	Binary	No	0
				Yes	1
Panel reactive antibody	Pre-transplant PRA	Pre-transplant PRA	continuous	n/a	
Creatinine	Creatinine (mmol/L)	Recipient creatinine prior to transplant	continuous	n/a	
Albumin	Albumin (g/L)	Recipient albumin prior to transplant	continuous	n/a	
Bilirubin	Bilirubin (mmol/L)	Recipient total bilirubin prior transplant	continuous	n/a	
Lactate	Lactate (mmol/L)	Recipient peak lactate immediately prior to ECMO implant	continuous	n/a	
CPB Time	Cardiopulmonary Bypass Time (min)	Cardiopulmonary Bypass Time (min)	continuous	n/a	
Ischemic Time	Total Ischemic Time (min)	Organ ischemic time	continuous	n/a	
Intra-op CABG	Intraoperative coronary artery bypass grafting	Intraoperative coronary artery bypass grafting	nominal	no	0
				yes	1
Desensitization therapy	Desensitization therapy used in the pre-op or intra-op period	Desensitization therapy	Binary	no	1
				yes	2
Induction immunosuppression	induction immunosuppression	induction immunosuppression	Nominal	none	1
				Thymoglobulin (ATG)	2
				Simulect (IL-2 antagonist)	3
				OKT3	4
Location of ECMO cannulation	Location of ECMO cannulation	Location where ECMO cannulation occurs	Nominal	Intro-op	1
				Post-op	2
Time to ECMO	Time to ECMO (hours)	Time from release of cross-clamp to ECMO cannulation	continuous	n/a	

ECMO cannulation site	ECMO cannulation configuration	ECMO cannulation configuration	Nominal	Central	1
				Peripheral	2
IABP co-therapy	IABP in addition to ECMO	IABP in addition to ECMO	Nominal	no	0
				yes	1
Impella co-therapy	Impella in addition to ECMO	Impella in addition to ECMO	Nominal	no	0
				yes	1
Surgical venting co-therapy	Surgical venting in addition to ECMO	Surgical venting in addition to ECMO	Nominal	no	0
				yes	1
Nitric oxide co-therapy	Nitric oxide in addition to ECMO	Nitric oxide in addition to ECMO	Nominal	no	0
				yes	1
Cause of graft dysfunction	Etiology of graft dysfunction indicating need for ECMO	Etiology of graft dysfunction	Nominal	primary graft dysfunction	1
				sepsis	2
				bleeding	3
				technical surgical complication	4
				hyperacute rejection	5
				pulmonary hypertension	6
				other	7
Time of first endomyocardial biopsy	Timing of first endomyocardial biopsy (days)	Timing of first endomyocardial biopsy from time of transplant in days	continuous	n/a	
Inotropes	Duration of IV Inotropic support postoperatively (days)	Duration of IV Inotropic support postoperatively (days)	continuous	n/a	
ICU Length of stay	ICU Length of stay (days)	Length of stay in ICU from time of transplant (days)	continuous	n/a	
ECMO explant	Explant of ECMO support	Explant of or weaning from ECMO support	Nominal	no	1
				yes	2
Death on ECMO	Death on ECMO support	Death on ECMO support	Nominal	no	1
				yes	2
ECMO support	Duration of ECMO support (days)	Duration of ECMO support (days)	continuous	n/a	
Bridged from ECMO	Bridged from ECMO to other therapy	Bridged from ECMO to other therapy	Nominal	not applicable	1
				BIVAD	2
				LVAD	3
				RVAD	4
				Re-transplant	5

Dialysis	Need for dialysis post-transplant	Need for dialysis post-transplant	Nominal	no	1
				yes	2
Time to dialysis	Time of dialysis initiation (hours)	Time of dialysis initiation from transplant (hours)	continuous	n/a	
ECMO complication	Complication experienced while on ECMO support	Complication experienced while on ECMO support	Nominal	Infection/sepsis	1
				Bleeding	2
				Limb ischemia with compartment syndrome or requiring amputation	3
				Stroke, embolic or hemorrhagic	4
				MOF	5
LVEF post-ECMO	LVEF on echo after ECMO decannulation	LVEF on echo after ECMO decannulation (%)	continuous	n/a	
Time of LVEF assessment	Time of LVEF assessment after ECMO explant	Time of LVEF assessment after ECMO explant (hours)	continuous		
Total length of stay	Length of stay from transplant to discharge (days)	Length of stay from transplant to discharge (days)	continuous	n/a	
Survival to hospital discharge	Survival to hospital discharge	Survival to hospital discharge	Nominal	no	1
				yes	2
Cause of death	Recipient Cause of Death	Recipient Cause of Death	Nominal	Other	1
				Multi Organ Failure	2
				Infection	3
				Graft Failure	4
				Renal Failure	5
				Acute Rejection	6
				Unknown	7
Time from transplant to death	Time from transplant to death if applicable	Time from transplant to death (days)	continuous	n/a	
Time from ECMO cannulation to death	Time from ECMO cannulation to death if applicable	Time from ECMO cannulation to death (days)	continuous	n/a	
Time post transplant	Time post transplant	Time post transplant (days)	continuous	n/a	
Last follow up	Last follow up	Last follow up (date-day/month/year)	continuous	n/a	

Appendix 2.3 Statistical plan for individual patient data meta-analysis

We will use a mixed effects logistic regression to model binary outcome variables (e.g., in-hospital mortality, VA-ECMO related bleeding) in which the log odds of the outcomes are modeled as a linear combination of the predictor variables when data are clustered or there are both fixed and random effects. We will not use fixed effects logistic regression because it may ignore necessary random effects in the data. We also cannot use logistic regression with clustered standard errors because this does not allow for random effects, which is necessary for an individual patient data meta-analysis.

One stage model with single covariate interactions for survival

We will conduct a one-stage model with single interactions with factors (or covariates) for prognosis. For survival to hospital discharge and survival to one-year, we will conduct a mixed effects logistic regression with each of the following factors individually, assuming that there is less than 20% missing data for each factor:

1) Recipient age (continuous)
2) Recipient sex (dichotomous)
3) Donor age (continuous)
4) Sex mismatch (female donor to male recipient, dichotomous)
5) Donor drug use (dichotomous)
6) Recipient-donor undersizing by weight and PHM
7) Pre-transplant temporary MCS (dichotomous)
8) Pre-transplant LVAD (dichotomous)
9) Pre-transplant dialysis (dichotomous)
10) Prior sternotomy (dichotomous)
11) Ischemic time (continuous)

One stage model with multiple covariate interactions for survival

For survival to hospital discharge and survival to one-year, we will conduct a mixed effects logistic regression with the following factors selected for their clinical importance in graft dysfunction, perioperative risk, and postoperative outcomes in heart transplantation:

1) Recipient age
2) Pre-transplant sternotomy
3) Ischemic time

Appendix 3.1 Reasons for non-availability of IPD by study authors who initially responded to our request

Study	Reason for non-availability of IPD
Zimpfer 2010	Significant delays with data transfer
Bittner 2011	No longer have access to data (different institution)
Hosmane 2012	Unable to provide data due to resource limitations
Loforte 2012	No longer have access to data (different institution)
Chou 2013	No reason provided
Santise 2014	No reason provided
Vallabhajosyula 2016	Registry data; not accessible for data-sharing
Xia 2016	No reason provided
Kobashigawa 2017	Data not retrievable
Takeda 2017	Significant delays with data transfer
Jolly 2018	Significant delays with data transfer
Mehta 2018	Unable to provide data due to resource limitations
Rajagopalan 2018	No longer have access to data (different institution)
DeRoo 2019	Significant delays with data transfer
Jacob 2019	No reason provided
Liao 2019	No reason provided
Nader 2019	No reason provided
Sastre 2019	No reason provided
Takeda 2019	Significant delays with data transfer
Zaleska-Kociecka 2019	Significant delays with data transfer
Becher 2020	Registry data; not accessible for data-sharing
Han 2020	Unable to provide data due to resource limitations
Mehdiani 2020	No reason provided

Appendix 3.2 Excluded studies

Study	Reason for exclusion
Groemmer 2009	Duplicate population of Zimpfer 2010
D'Alessandro 2010	Overlapping population with D'Alessandro 2011, which is more comprehensive study
Chen 2010	Overlapping population in Chou 2010
Chou 2010	Overlapping population in Chou 2013
Kittleson 2011	Wrong study population, time to VA-ECMO was 3 to 12 months after HT
Spada 2011	Overlapping population in Loforte 2016
Bittner 2013	Overlapping population with Bittner 2011
Raffa 2013	Overlapping population with Santise 2014
Santise 2013	Overlapping population with Santise 2014
Chen 2014	Overlapping population with Chou 2010 and Chou 2013
Muehle 2014	Duplicate population of Lehmann 2014
Huang 2016	Duplicate population of Connolly 2019
Li 2016	Duplicate population of Takeda 2017
Loforte 2016	Overlapping population in Loforte 2015, which is more comprehensive
Raffa 2016	Overlapping population in Santise 2014, which is more comprehensive
Boeken 2017	Duplicate population of Boeken 2018
Chang 2017	Overlapping population of Kobashigawa 2017
DeRoo 2017	Duplicate population of DeRoo 2019
Garcia-Gigorro 2017	Wrong outcomes; no report of mortality
Rajagopalan 2017	Duplicate population of Rajagopalan 2018
Sabatino 2017	Overlapping study population in Santise 2014 and Loforte 2015

Boeken 2018	Duplicate population of Mehdiani 2020
Lehmann 2018	Abstract only; presents data on additional patients but not as trustworthy as full text Lehmann 2014
Tran 2018	Wrong study population: time to VA-ECMO included after index hospitalization for HT
Chew 2019	Overlapping population with Connolly 2019
Jaamaa-Holmberg 2019	Wrong study population; pre-transplant VA-ECMO
Lopez Vilella 2019	Wrong study population; pre-transplant VA-ECMO
Patel 2019	Overlapping population of Kobashigawa 2017
Fiorentino 2020	Overlapping population with Loforte 2016
Noly 2020	Overlapping population in Hebert 2017 and Nader 2019 which present both populations more completely