A Systematic Review for Variables to Be Collected in a Transplant Database for Improving Risk Prediction

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Background. This systematic review was commissioned to identify new variables associated with transplant outcomes that are not currently collected by the Organ Procurement and Transplantation Network (OPTN). **Methods.** We identified 81 unique studies including 1 193 410 patients with median follow-up of 36 months posttransplant, reporting 108 unique risk factors. **Results.** Most risk factors (104) were recipient related; few (4) were donor related. Most risk factors were judged to be practical and feasible to routinely collect. Relative association measures were small to moderate for most risk factors (ranging between 1.0 and 2.0). The strongest relative association measure for a heart transplant outcome with a risk factor was 8.6 (recipient with the previous Fontan operation), for a kidney transplant 2.8 (sickle cell nephropathy as primary cause of end-stage renal disease), for a liver transplant 14.3 (recipient serum ferritin >500 μg/L), and for a lung transplant 6.3 (*Burkholderia cepacia* complex infection for 1 y or less). OPTN may consider some of these 108 variables for future collection to enhance transplant research and clinical care. **Conclusions.** Evidence-based approaches can be used to determine variables collected in databases and registries. Several candidate variables have been identified for OPTN.

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INTRODUCTION

Organ transplant is a major clinical procedure that requires shared decision-making and accurate risk prediction. Therefore, it is critical to know which recipient and donor variables affect transplant outcomes. Databases and registries that track transplants collect variables with the goal of improving process measures and ultimately leading to better patient outcomes and higher quality of care. Such variables have been collected based on prior research and expert opinion. In the United States, the Organ Procurement and Transplantation Network (OPTN) database has grown in both size and importance. The legal framework for the database was established by the National Organ Transplantation Act.[1] Transplantation

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under National Organ Transplantation Act is administered by the US Department of Health and Human Services, Health Resources and Services Administration (HRSA), Division of Transplantation. HRSA is supported by 2 contracts, one for OPTN, which collects and administers the database, and another for the Scientific Registry of Transplant Recipients (SRTR),[2] which provides analysis of OPTN data. HRSA contracts with not-for-profit foundations to administer and maintain the database.

In 1999, the Final Rule for governing OPTN and its database were published in the US Registry,[3] stipulating that "The OPTN and the Scientific Registry, as appropriate, shall: (1) Maintain and operate an automated system for managing information about transplant candidates, transplant recipients, and organ donors, including a computerized list of individuals waiting for transplants, (2) Maintain records of all transplant candidates, all organ donors and all transplant recipients, (3) Operate, maintain, receive, publish, and transmit such records." The SRTR Technical Advisory Committee recommended a process to review, add, or remove data elements, based on pilot studies that demonstrated a contribution to the model, and that the data management process should proceed in a continuous or cyclical timeframe. However, controversy has continued as to whether OPTN is collecting adequate data needed to adjust models that calculate transplant program expected outcomes. In 2012, a consensus conference was held to discuss the use of OPTN data for quality assurance by OPTN, the Centers for Medicare & Medicaid Services (CMS), and private insurance providers. Recommendations included collecting more reliable organ-specific data on coronary heart disease (eg, revascularizations), peripheral vascular disease (eg, revascularizations and amputations), diabetes mellitus, zip code socioeconomic status, donor risk, and ventricular assist devices.[4]

To better inform the question of whether additional OPTN data elements might improve risk prediction models for posttransplant outcomes,[5] SRTR collaborated with the Mayo Clinic Agency for Healthcare Research and Quality Evidence Practice Center[6] to conduct a systematic review. The systematic review targeted published multivariate analyses of pretransplant risk factors, including donor and recipient factors, and patient-level and system-level factors predicting outcomes of importance to patients (eg, death and allograft survival). The transplanted organs evaluated were kidney, pancreas, liver, heart, and lung. The review also evaluated multiorgan transplants such as simultaneous heart-lung, kidney-pancreas, and kidney-liver transplants. The systematic review was designed to identify risk factors that are not currently being collected.

MATERIALS AND METHODS

The reporting of this systematic review adheres to the Preferred Reporting for Systematic Reviews and Meta-Analysis statement.[7] The study protocol was developed and executed by methodologists with expertise in evidence synthesis and SRTR staff who provided clinical and contextual expertise.

Data Sources and Search Strategies

A comprehensive search of several databases from the inception of each to November 16, 2016, was conducted. The databases included the Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus. Grey literature and conference abstracts were also searched. The search strategy was designed and conducted by a medical reference librarian with input from the investigators. Controlled vocabulary supplemented with keywords was used to search for studies of risk factors for outcomes of kidney, pancreas, liver, heart, lung, and combined transplants. Details of the strategy are described in the Supporting Information.

Main Outcome Measure

Outcomes of interest were death on the waiting list, all-cause mortality, graft failure, death-censored graft loss, and waitlist mortality (death/delisting due to being too sick to undergo transplant). Risk factors for each organ transplant failure outcome were reported with odds ratio, hazard ratio (HR), and relative risk, which were extracted and were all referred to as relative effect. Only risk factors that were significantly associated with the outcome were extracted. Due to the vast heterogeneity of the risk factors and outcomes and the scarcity of studies representing each individual risk factor, a meta-analysis was not feasible.

Study Selection

We included studies that evaluated risk factors of transplant (donor and recipient factors, patient-level and system-level factors, only preoperative factors, organs: kidney, pancreas, pancreas + kidney, liver, liver + kidney, heart, lung, and heart + lung). Risk factors were obtained from studies in which patients were eligible for organ transplant, were waitlisted for deceased donor transplant, or underwent deceased donor/living donor transplant.

We did not restrict time or study location. We included randomized controlled trials and observational studies. Systematic reviews and meta-analyses were initially included for cross-referencing. We excluded editorials, letters, narrative and systematic reviews, and errata, as well as non-English publications. We included studies based on the following sample size criteria: kidney alone ≥ 1000 patients, pancreas ≥ 100, pancreas + kidney ≥ 100, liver alone ≥ 100, liver + kidney ≥ 50, heart ≥ 100, lung ≥ 100, and heart + lung any sample size. These organ-specific sample-size thresholds were chosen in order to exclude small studies that would likely be underpowered to detect any effects of risk factors on the outcome(s) under study while still including as many studies as possible in the analysis.

We excluded studies focused on human leukocyte antigen compatibility as a risk factor, and studies focused on risk factors obtained solely from the OPTN database without additional data sources.

Seven independent reviewers screened the abstracts and full text of eligible references in duplicates. Discrepancies between pairs of reviewers were handled through discussions and consensus. If consensus was not reached, a third reviewer was asked to resolve the difference.

Data Extraction and Risk of Bias Assessment

A pilot-tested standardized data extraction form was created. The following information was extracted: author, sample size, organ (to be) transplanted, whether patients were on the transplant waiting list or had undergone

transplant, outcomes and associated risk factors, and follow-up duration. Risk of bias was assessed for each included study using the following items, derived from the Newcastle-Ottawa scale[8]: single center versus multicenter, cohort selection, outcome ascertainment, adjusting the analysis, and loss to follow-up. Based on these factors, the risk of bias for each study was low, moderate, or high. Data extraction and risk of bias were performed by pairs of independent reviewers.

RESULTS

Study Characteristics

The search strategy identified 4909 relevant citations. A total of 81 unique studies with an average sample size of 14 733 patients met the inclusion criteria (Figure 1). Thirty-four studies were conducted in the United States. Median follow-up was 36 months posttransplant (range 1–130). Table S1 (**SDC**, http://links.lww.com/TP/B695) lists the characteristics of included studies.

Risk of Bias

Most included studies had a retrospective cohort design. Only a few (6 [7%]) were prospective. Risk of bias assessment for the included studies is listed in Table S3 (**SDC**, http://links.lww.com/TP/B695). Overall, the risk of bias was low to moderate for most factors due to adequate follow-up, outcome ascertainment, and multivariable adjustment.

Variables to Be Collected in Transplant Databases

One hundred eight unique risk factors were found which are not currently included in the OPTN database. Most (104) were recipient related and very few (4) were donor related. Risk factors overlapped somewhat by organ. The highest number of new risk factors related to liver transplant (14 recipient related for patients on the waiting list, 30 recipient related for patients who underwent the transplant, and 1 donor related). The next highest number related to kidney transplant (1 recipient related for patients on the waiting list, 29 recipient related for patients who underwent transplant, and 1 donor related). Regarding heart transplant, 5 risk factors were recipient related for patients on the waiting list, 10 were recipient related for patients who underwent transplant, and 2 were donor related. Fewer data were available for lung transplant (4 recipient-related risk factors for patients on the waiting list, 9 for patients who underwent transplant) and pancreas transplant (1 donor related).

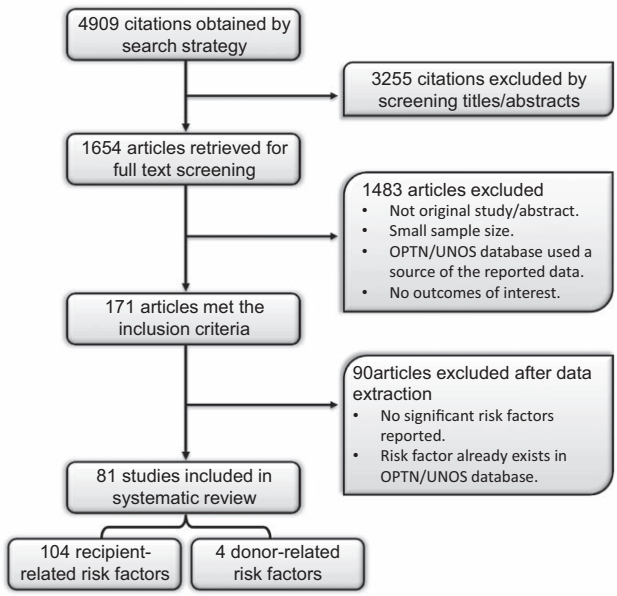

FIGURE 1. Flowchart depicting the process of study selection. OPTN, Organ Procurement and Transplantation Network; UNOS, United Network for Organ Sharing.

Table 1 lists the risk factors for each organ transplant for patients on the waiting list, and Table 2 for patients who underwent transplant. Table 3 lists the donor-related risk factors for each organ. More details about the studies assessing risk factors are outlined in Table S2 (**SDC**, http://links.lww.com/TP/B695). These tables provide information on the size of the relative effect that associates the risk factor with the outcome, the type of outcome, lengths of follow-up, and risk of bias. Some variables are impractical or difficult to routinely collect (eg, heart failure survival score and Framingham stroke risk profile). The majority of risk factors were adjusted in multivariable regression models implemented in each study (with some variabilities in the adjusted factors among the individual studies) as indicated in Tables S2.1 and S2.2 (**SDC**, http://links.lww.com/TP/B695).

Magnitude of Association

Most of the relative association measures (odds ratios, relative risks, or HRs) ranged between 1.0 and 2.0 (mild-to-moderate association), with just a few suggesting a strong association.

As for the recipient-related risk factors, the strongest relative association for a heart transplant outcome with a risk factor was 8.6 (association between all-cause mortality and a previous Fontan operation). Five risk factors for heart transplant outcomes had a low likelihood of bias (association between death on the waiting list and the recipient not using β-blockers, association between death on the waiting list and lower recipient heart failure survival score, association between death on the waiting list and recipient nonsustained ventricular tachycardia, association between all-cause mortality and recipient myocarditis, and association between all-cause mortality and lower recipient left ventricular end-diastolic dimension z score). The strongest relative association with a low likelihood of bias for a heart transplant outcome with a risk factor was 2.7 (association between all-cause mortality and recipient myocarditis).

The strongest relative association for a kidney transplant outcome with a risk factor was 2.8 (association between all-cause mortality and sickle cell nephropathy as the primary cause of end-stage renal disease). This risk factor had a moderate likelihood of bias. The strongest relative association with a low likelihood of bias for a kidney transplant outcome with a risk factor was 2.2 (association between all-cause mortality and recipient smoking).

The strongest relative association for a liver transplant outcome with a risk factor was 14.3 (association between waitlist mortality and serum ferritin >500 μg/L). This risk factor also had a low likelihood of bias.

TABLE 1.

Recipient-related risk factors for patients registered on the transplant waiting list

Risk factor	Included studies	Total number of patients	Follow-up (mo)	Outcome	Relative effect	Likelihood of bias
Heart						
Patient not on β-blockers	Sandner et al[9]	854	4.7	Death on the waiting list	1.82	Low
Heart failure Survival Score[a]	Zahn et al[10]	318	12	Death on the waiting list	0.64	Low
Nonhypoplastic left heart syndrome	Guleserian et al[11]	694	60	Death on the waiting list	1.79	Moderate
Nonsustained ventricular tachycardia	Sandner et al[9]	854	4.7	Death on the waiting list	1.76	Low
Prostaglandin-dependent hypoplastic left-sided heart syndrome	Morrow et al[12]	118	6	Death on the waiting list	1.48	High
Kidney						
Central venous catheter placement	Hernández et al[13]	3851	22	Death on the waiting list	1.70	Moderate
Liver						
Anaerobic threshold during cardiopulmonary exercise testing[b]	Ow et al[14]	164	3	Death on the waiting list	0.73	Moderate
Peak V_{o2} during cardiopulmonary exercise testing[b]	Ow et al[14]	164	3	Death on the waiting list	0.75	Moderate
Median income < $60 244	Schwartz et al[15]	147	32.5	Death on the waiting list	1.35	High
Severely malnourished by subjective global assessment	Ferreira et al[16]	159	8.85	Death on the waiting list	2.60	Low
Fried frailty score (per point increase)[a]	Lai et al[17]	294	12	Waitlist mortality[c]	1.45	Low
Instrumental Activities of Daily Living scale (per point decrease)[a]	Lai et al[17]	294	12	Waitlist mortality	1.17	Low
Results of short physical performance battery (per point decrease)	Lai et al[17]	294	11.33	Waitlist mortality	1.19	Low
Recurrent spontaneous peritoneal bacterial infection[d]	Silberhumer et al[18]	505	35	Death on the waiting list	1.59	Moderate
Lack of previous ursodeoxycholic acid treatment in patients with PSC	Brandsaeter et al[19]	255	NR	Death on the waiting list	5.00	Low
Brain failure	Reddy et al[20]	136	6	Waitlist mortality	3.40	High
Circulatory failure	Reddy et al[20]	136	6	Waitlist mortality	6.11	High
Respiratory failure	Reddy et al[20]	136	6	Waitlist mortality	5.26	High
Infections other than urinary tract infection	Reddy et al[20]	136	6	Waitlist mortality	3.33	High
Serum ferritin > 500 μg/L	Walker et al[21]	322	12	Waitlist mortality	14.3	Low
Serum ferritin > 400 μg/L					3.49	
Lung						
Nonaccredited cystic fibrosis center	Belkin et al[22]	343	NR	Death on the waiting list	2.00	High
Cystic fibrosis patients without *Staphylococcus aureus* pneumonia[e]	Liou et al[23]	248	NR	Death on the waiting list	1.46	High
Mixed venous oxygen saturation during exercise (SvO)	Selimovic et al[24]	177	NR	Waitlist mortality	0.95	Low
Pulmonary vascular resistance (wood units)	Selimovic et al[24]	177	NR	Waitlist mortality	1.23	Low

[a]Not practical to collect.
[b]mL/min/kg, per unit.
[c]Waitlist mortality: death/delisting for being too sick for transplant.
[d]The need for hospitalization because of increased infection parameters combined with leucocyte positive ascites.
[e]Likely due to active competition between *Staphylococcus aureus* and more harmful *Pseudomonas aeruginosa*.
NR, not reported; PSC, primary sclerosing cholangitis.

TABLE 2.

Recipient-related risk factors for patients who underwent transplant

Risk factor	Included studies	Total number of patients	Follow-up (mo)	Outcome	Relative effect	Likelihood of bias
Heart						
Left ventricular end-diastolic dimension z score[a]	Pietra et al[25]	209	<48	All-cause mortality	1.19	Low
Mean right atrial pressure at pretransplant cath (13 vs 5)	Tallaj et al[26]	7015	71	All-cause mortality	1.2	Moderate
History of poor compliance[b]	Owen et al[27]	108	32.3	All-cause mortality	3.4	Moderate
Preoperative cachexia[b]	Grady et al[28]	4515	48	All-cause mortality	NR	Moderate
Intubation before transplant	Zuckermann et al[29]	702	61.2	All-cause mortality	NR	Moderate
Myocarditis at diagnosis	Pietra et al[25]	209	<48	All-cause mortality	2.71	Low
Ischemic heart disease[b]	Lindelöw et al[30]	113	67.2	Graft failure[c]	5.8	Moderate
Pretransplant *Toxoplasma gondii* seropositivity	Arora et al[31]	246	66	All-cause mortality	1.93	Moderate
Previous classical Glenn operation	Lamour et al[32]	488	27.6	All-cause mortality	3.1	High
Previous Fontan operation	Lamour et al[32]	488	27.6	All-cause mortality	8.6	High
Kidney						
Comorbidity[b]	Anderson et al[33]	171 180	NR	All-cause mortality	2.02	Moderate
	Laskin et al[34]		100.8		1.28	Moderate
	Barrantes et al[35]		48.4		1.18	Moderate
	Goldfarb-Rumy-antzev et al[36]		NR		1.1	Moderate
	Gueye et al[37]		NR		1.18	Moderate
Comorbidity[b]	Laskin et al[34]	157 214	100.8	Graft failure	1.25	Moderate
	Goldfarb-Rumy-antzev et al[36]		NR		1.06	Moderate
	Gueye et al[37]		84		1.09	Moderate
Charlson comorbidity score[bd]	Barrantes et al[35]	1064	48.4	Death-censored graft loss	1.18	Moderate
Angina pectoris[b]	Aalten et al[38]	130 914	96	All-cause mortality	2.03	Moderate
	Gill and Pereira[39]		≥12		1.38	Moderate
	Petersen et al[40]		NR		1.33	Moderate
History of cardiovascular disease[b]	Patzer et al[41]	135 636	36	All-cause mortality	1.47	High
	Petersen et al[40]		NR		1.41	Moderate
	Laging et al[42]		48		2.5	Moderate
Congestive heart failure	Browne et al[43]	2776	24	Graft failure	1.48	High
Myocardial infarction	Farrugia et al[44]	124 284	52.8	All-cause mortality	1.52	Low
	Petersen et al[40]		NR		1.31	Moderate
Cardiac failure	Petersen et al[40]	105 181	NR	All-cause mortality	1.36	Moderate
Claudication	Aalten et al[38]	2187	3	All-cause mortality	1.55	Moderate
Coronary artery disease	Petersen et al[40]	105 181	NR	All-cause mortality	1.35	Moderate
Dysrhythmia	Petersen et al[40]	105 181	NR	All-cause mortality	1.45	Moderate
				Death-censored graft loss	1.26	
History of stroke	Ferro et al[45]	19 103	52.8	All-cause mortality	1.8	Low
Ischemic heart disease	Petersen et al[40]	105 181	NR	All-cause mortality	1.28	Moderate
Cardiac failure	Petersen et al[40]	105 181	NR	Death-censored graft loss	1.14	Moderate
Pretransplant cardiovascular risk score (per 1 score increase) (Framingham risk score)	An et al[46]	2902	76.8	Graft failure	1.05	Moderate
Cardiovascular disease	Petersen et al[40]	105 181	NR	Death-censored graft loss	1.12	Moderate
History of cardiovascular disease (third tertile in CV risk score)	An et al[46]	2902	76.8	Graft failure	1.65	Moderate
Residence in deprived areas	Ferro et al[45]	19 103	52.8	All-cause mortality	1.48	Low
Socioeconomic status estimated by median household income quartile (high-mid quartile vs lower quartile)	Foster et al[47]	90 689	12	Death-censored graft loss	0.91	Moderate

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TABLE 2. (Continued)

Risk factor	Included studies	Total number of patients	Follow-up (mo)	Outcome	Relative effect	Likelihood of bias
Residence in mild deprived area (4) vs residence in least deprived area (5)	Ferro et al[45]	19 103	52.8	All-cause mortality	1.21	Low
Residence in moderate deprived area (3) vs residence in least deprived area (5)	Farrugia et al[44]	19 103	52.8	All-cause mortality	1.43	Low
Residence in most deprived area (2) vs residence in least deprived area (5)	Ferro et al[45]	19 103	52.8	All-cause mortality	1.25	Low
Chronic opioid usage	Barrantes et al[35]	1064	48.4	All-cause mortality	1.65	Moderate
Smoking[e]	An et al[46]	2902	76.8	Graft failure	1.58	Moderate
Smoking	Arend et al[48]	916	240	All-cause mortality	2.2	Low
Sickle cell nephropathy vs all other primary causes of end-stage renal disease	Ojo et al[49]	22 647	36	All-cause mortality	2.82	Moderate
				Death-censored graft loss	1.6	
>5 lifetime blood transfusions[b]	Benfield et al[50]	4898	60	Graft failure	1.6	High
Ratio of the weight of the kidney to the weight of the recipient <2.3 g/kg[b]	Giral et al[51]	1060	74.4	Graft failure[f]	1.51	Moderate
Proteinuria (severe vs mild)	Pavlakis et al[52]	126	36	Graft failure	2.54	High
Liver						
Microvascular invasion of HCC	Wang et al[53]	1026	33	All-cause mortality	3.1	High
	Marques et al[54]		34		2.39	High
	Moon et al[55]		60		4.84	High
	An et al[56]		28.3		2.69	Moderate
	Silva et al[57]		12		3.02	Moderate
Macrovascular invasion of HCC	Iwatsuki et al[58]	344	120	All-cause mortality	3.5	Moderate
HCC differentiation grade	Wang et al[53]	238	33	All-cause mortality	1.8	High
Sarcopenia[b]	Masuda et al[59]	328	12	All-cause mortality	2.06	High
	Kaido et al[60]		12		4.85	High
Fulfill Hangzhou criteria (deceased donor liver transplantation group)	Chen et al[61]	94	41.5	All-cause mortality	3.29	Moderate
Fulfill Hangzhou criteria (living donor liver transplantation group)	Chen et al[61]	47	41.5	All-cause mortality	9.16	Moderate
Serum albumin	Zhang et al[62]	241	43.6	All-cause mortality	6.33	Moderate
	Nuño et al[63]		1		NR	Moderate
Graft/recipient weight ratio[b]	Yi et al[64]	766	32.6	All-cause mortality	200	Moderate
	Elgend et al[65]		60		NR	
Left ventricular hypertrophy	Darstein et al[66]	492	50.4	All-cause mortality	1.42	Moderate
	Batra et al[67]		20		5.92	
Red cell units transfusion[b]	Parikh et al[68]	659	1	All-cause mortality	1.04	Moderate
	Boyd et al[69]		36		1.03	Low
Red cell transfusion	Parikh et al[68]	450	1	Graft failure	1.04	Moderate
CRP ≥ 1 mg/dL	An et al[56]	85	28.3	All-cause mortality	2.68	Moderate
Encephalopathy grade 4 vs grade 0	Lewsey et al[70]	4829	3	All-cause mortality	2.51	High
Estimated glomerular filtration rate	Li et al[71]	218	3	All-cause mortality	NR	Moderate
Hypertriglyceridemia[g]	Beckebaum et al[72]	104	64.1	All-cause mortality	1.01	Moderate
Hypertriglyceridemia[g]	Beckebaum et al[72]	104	64.1	Graft failure	1.01	Moderate
Ishak fibrosis score > 3	Belli et al[73]	502	60	All-cause mortality	4.91	Low
Lifestyle activity score 5 vs score 1[h]	Lewsey et al[70]	4829	3	All-cause mortality	2.23	High
Beta natriuretic peptide, per 50 pg/mL increase[b]	Toussaint et al[74]	207	6	All-cause mortality	1.035	Moderate
Pretransplant intramuscular adipose tissue content[b]	Hamaguchi et al[75]	200	12	All-cause mortality	3.9	Low
Pretransplant PMI[bi]	Hamaguchi et al[75]	200	12	All-cause mortality	3.64	Low
Preoperative uncontrollable hydrothorax and massive ascites	Endo et al[76]	237	36	All-cause mortality	2.3	Moderate
Serum choline esterase < 2.6 kU/L[b]	Weismüller et al[77]	462	12	All-cause mortality	1.71	Low
Serum ferritin concentration > 365 µg/L and transferrin saturation < 55%	Weismüller et al[78]	328	42	All-cause mortality	1.9	Low
Serum potassium (mmol/L) >5.0 vs <3.5	Dawwas et al[79]	5942	60	All-cause mortality	1.38	Low

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TABLE 2. (Continued)

Risk factor	Included studies	Total number of patients	Follow-up (mo)	Outcome	Relative effect	Likelihood of bias
Serum potassium (mmol/L) 4.5–5.0 vs <3.5	Dawwas et al[79]	5942	60	All-cause mortality	1.47	Low
Pretransplant serum Mg (<1.8 mg/dL)	Elgend et al[65]	673	60	Graft failure	2.36	Moderate
Intubation before transplant	Parikh et al[68]	450	1	Graft failure	2.41	Moderate
High pretransplant BUN	Elgend et al[65]	673	60	Graft failure	1.05	Moderate
Pretransplant platelet count	Elgend et al[65]	673	60	Graft failure	NR	Moderate
Lung						
Atrial fibrillation	Plantier et al[80]	258	13.2	All-cause mortality	3.51	Low
Carotid atheroma[b]	Plantier et al[80]	258	13.2	All-cause mortality	1.49	Low
Burkholderia cepacia pneumonia	Stephenson et al[81]	580	60	All-cause mortality	1.92–6.29	Low
Executive function	Smith et al[82]	201	129.6	All-cause mortality	1.09	Moderate
Impaired memory	Smith et al[82]	201	129.6	All-cause mortality	1.11	Moderate
Framingham stroke risk profile[b]	Smith et al[82]	201	129.6	All-cause mortality	1.13	Moderate
Pancreatic sufficiency	Stephenson et al[81]	580	60	All-cause mortality	2.13	Low
Serum prealbumin ≤ 18 g/dL[b]	González-Castro et al[83]	112	NR	All-cause mortality	3.01	Moderate
Cystic fibrosis patients with *Staphylococcus aureus* pneumonia	Liou et al[23]	248	NR	All-cause mortality	1.51	High

[a]The increased risk is associated with a lower score.
[b]Not practical to collect.
[c]Graft coronary artery disease.
[d]A lower Charlson comorbidity is associated with a higher risk of graft loss.
[e]Relative risk has been calculated based on the raw data that corresponds to current smoking vs never smoked.
[f]Graft failure after 2 years follow–up.
[g] Defined as fasting total cholesterol level of 200 mg/dL or the need for antilipemic agents.
[h] Clinician reported measure on a 5-point score of the impact of disease on the ability to carry out activities of daily living.
[i]The increased risk of mortality is related to low pretransplant PMI.
BUN, blood urea nitrogen; CV, cardiovascular; CRP, C-reactive protein; HCC, hepatocellular carcinoma; NR, not reported; PMI, psoas muscle mass index.

TABLE 3.

Donor-related risk factors

Risk Factor	Included studies	Total number of patients	Follow-up (mo)	Outcome	Relative effect	Likelihood of bias
Heart						
Coronary atherosclerosis of the donor heart (double- or triple-vessel coronary atherosclerosis vs single or no vessel coronary atherosclerosis)	Grauhan et al[84]	1168	120	All-cause mortality	11.5	High
Hormonal therapy in donor	Conway et al[85]	3149	1	All-cause mortality	1.52	Moderate
Kidney						
Donor's acute kidney injury stage 1, 2, or 3 vs no AKI	Boffa et al[86]	11 219	12	Graft failure	1.2	Low
Pancreas						
Donor hyperglycemia (glucose ≥200 vs <200 mg/dL)	Gores et al[87]	253	12	Graft failure	1.4	Moderate

AKI, acute kidney injury.

The strongest relative association for a lung transplant outcome with a risk factor was 6.3 (association between all-cause mortality and the recipient having *Burkholderia cepacia* complex for 1 y or less). This risk factor also had a low likelihood of bias.

Regarding donor-related risk factors, the strongest relative association for a heart transplant outcome with a risk factor was 11.5 (association between all-cause mortality and coronary atherosclerosis of the donor heart with double- or triple-vessel coronary atherosclerosis versus single- or no-vessel coronary atherosclerosis). The only relative association for a kidney transplant outcome with a risk factor was 1.2 (association between graft failure and donor acute kidney injury stage 1, 2, or 3 versus no acute kidney injury). This risk factor also had a low likelihood of bias. The only relative association for a pancreas transplant outcome with a risk factor was 1.4 (association between graft failure and donor hyperglycemia [glucose ≥ 200 mg/dL versus < 200 mg/dL]).

DISCUSSION

Main Findings

This systematic review demonstrates that additional recipient and donor data elements not collected in the

OPTN database are associated with recipient and allograft outcomes posttransplant and candidate survival on the waiting list. Recipient data elements for kidney transplant include central venous catheter use at time of listing, and comorbid conditions (especially cardiovascular), socioeconomic factors, and smoking status at time of transplant. For liver transplant, recipient data elements include physiological parameters, socioeconomic status, comorbid conditions at time of listing, and functional capacity at time of transplant. For lung transplant, recipient data elements include infections and physiological parameters at time of listing and comorbid conditions, functional status, and infections at time of transplant. For pancreas transplant, recipient data elements include comorbid conditions at time of transplant. For heart transplant, recipient data elements include heart disease-related factors at time of listing, physiological parameters, and heart disease-related factors at time of transplant. Fewer donor-related data elements not collected in the OPTN database were identified. These include donor comorbid conditions and donor allograft characteristics. The present systematic review summarizes the entire body of evidence for these additional variables and presents an opportunity to add these variables to the registry.

Practical Implications

In the past, data elements have been added in an ad hoc fashion through OPTN's organ-specific committees. Based on HRSA guidance, a Data Advisory Committee was established by OPTN/United Network for Organ Sharing (UNOS) with the purview of assessing the quality of data collected by OPTN. If OPTN decides to incorporate any of the identified additional risk factors, the next step would be to assess feasibility of collecting these data elements in an objective fashion. The use of robust definitions is imperative for any new data collection. The Data Advisory Committee, in concert with OPTN/UNOS organ-specific committees, could also assess the unintended consequences of use of any new data variables prior to recommending data collection by OPTN/UNOS. The criticism that OPTN/UNOS will encounter relates to the additional data collection burden on transplant providers.

Because some of these variables occur at the time of listing, the cost of collection may be covered by the transplant program hospital cost report as funded by CMS.[88] However, the cost of collecting data at the time of transplant has sometimes been deemed an "unfunded mandate." Recently, awareness has been growing in the transplant community that the data collected by OPTN are not adequate, especially when used to assess outcomes for transplant program quality assurance.[4] These 2 competing concerns will likely need to be balanced. One way to balance them is to remove from the existing OPTN data risk factors that are not reliably collected or are not associated with outcomes.

Another criticism that OPTN/UNOS is likely to encounter is that comorbid conditions are available on form CMS-2728 and in CMS claims. However, these data are not readily available to transplant programs. Also, CMS data are available only after substantial lag time, and CMS claims are not available for patients for whom Medicare is not the primary insurer.

Several comorbid conditions identified in this systematic review occurred at the time of transplant as risk factors for posttransplant kidney allograft outcomes. These were assessed using multivariate modeling and include history of stroke (HR, 1.80; 95% confidence interval [CI], 1.39–2.33),[45] acute myocardial infarction (HR, 1.52; 95% CI, 1.15–1.84),[44] and claudication (HR, 1.55; 95% CI, 1.05–2.29).[38] Several other studies corroborated this association of cardiovascular and peripheral vascular conditions.[39,40,42,89] Some studies went a step further and combined comorbid conditions as indices, finding that presence of one or more condition in the comorbidity indices was associated with increased risk of worse posttransplant allograft outcomes.[33-35,37] Similarly, conditions such as left ventricular hypertrophy,[66,67] low glomerular filtration rate,[71] hypertriglyceridemia,[72] hypercholesterolemia[72]; malnutrition-related factors such as low albumin[62,63] or intramuscular adipose tissue content[75]; and psoas muscle mass index[75] or low muscle mass[60,75] emerged as important risk factors for liver transplant. Conditions such as atrial fibrillation,[80] carotid atheroma,[80] stroke risk,[82] pancreatic insufficiency,[81] and infections[23,81] were risk factors for lung transplant. Conditions such as congestive heart failure[43] and proteinuria[52] were important risk factors for pancreas transplant. Conditions such as previous cardiac operations,[32] cerebral vascular accident,[90] and malnourishment as evidenced by low albumin[90,91] or preoperative cachexia[28] were risk factors for heart transplant.

Socioeconomic status was another risk factor category at time of transplant, associated with post-kidney transplant outcomes. Socioeconomic status was defined as residence in a most deprived area[44,45] or as median household income by zip code.[47] Similarly, the median income at time of listing was a risk factor for liver transplant.[15]

Some risk factors were unique to the specific type of organ transplant. Preoperative pulmonary vascular resistance index[92] and left ventricular end-diastolic dimension[25] were identified as physiological risk factors associated with post-heart transplant outcomes. Hepatocellular carcinoma–related risk factors such as microvascular invasion,[54-58] C-reactive protein,[56] Milan criteria,[58,61,72] intrahepatic metastasis,[55] and cancer differentiation grade[53] were associated with post-liver transplant outcomes, as were intraoperative risk factors such as number of red blood cell transfusions.[68] Functional capacity defined by executive function[82] or memory[82] was associated with post-lung transplant outcomes.

Fewer risk factors were identified at time of listing than at time of transplant, but the types of risk factors were similar in theme. For example, the same comorbid conditions were important risk factors at time of listing and time of transplant. For practitioners, knowing risk factors that affect patient prognosis is important for shared decision-making. Such risk factors can be discussed with patients contemplating transplant to shape their expectations and keep them more informed about prognosis. If risk factors were modifiable, this knowledge gives patients and clinicians the opportunity to institute preventive measures.

Limitations and Strengths

The quality of evidence is limited due to deriving estimates from retrospective or single-center studies with

heterogeneous data reporting. Some studies provided unadjusted estimates. Some variables, whether already collected by OPTN or identified in this review, can be codependent or collinear or have statistical interactions. These statistical associations should be assessed in future studies conducting multivariable analyses of OPTN data, and they cannot be determined in this systematic review. In addition, once new variables have been collected, future research is needed to study how the new variables and their interactions with existing variables affect risk prediction.

To our knowledge, this report provides the most comprehensive review of risk factors for death and allograft survival for solid organ transplants. These results can serve as a rationale for adjusting data elements currently being collected and may help providers engage patients in shared decision-making at the time of listing and of transplant. We hope that this model (a systematic review to determine which data elements should be included in registries and databases) can be extended to registries of other conditions and clinical fields.

A need remains for unambiguous definitions to accompany future refinement of OPTN/UNOS data collection, along with uniform reporting of risk factors and outcomes. These risk factors can fuel optimal care of solid organ transplant patients through their use in quality improvement tools provided by SRTR to all transplant programs. Adequate collection of risk factors can encourage providers to perform transplants in patients with these risk factors and innovate to reduce the negative impact of these risk factors, because the SRTR models could account for them.

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