Long-Term Mortality Following Inter-hospital Transfer for Acute Myocardial Infarction: An Observational Cohort Study

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Supplementary Appendix

Contents

1. Variables considered in the propensity analysis

1A. Variables included in the propensity score analysis

(1) Demographic characteristics and diagnosis at index presentation as coded in the New South Wales admitted patient data collection (NSWAPDC). These specifically include age at admission, sex, proportion of patients using private health insurance cover, admission year, and principle ICD10AM diagnosis at index presentation

(2) Variables encompassing past cardiac history and comorbidities at presentation derived from index admission and admissions occurring within the 12 months immediately preceding the date of index hospitalization (see below)

(3) Variables encompassing acute complications typical of AMI admission derived from secondary diagnosis codes at the initial presenting hospital at index hospitalization (see below)

(4) Variables encompassing hospital service/capacity and hospital region- diagnostic angiography and revascularization capability, region (major cities vs. regional or remote hospitals) and hospital peer group category. The Australian hospital peer group categories classify all public hospitals based on size and number of case mix adjusted acute presentations and are categorized as principle referral, large, medium and small acute hospitals. Private hospitals are not categorized based on this classification and therefore are recorded as private hospitals only.

Variables representing patient past cardiac history and comorbidities were derived from the administrative diagnostic codes assembled in to condition categories (CC) which group clinically coherent diagnostic codes into single variables. The CC candidate variables considered for this analysis were derived from the secondary diagnosis and procedure codes from the index hospitalization and from the principal and secondary ICD10AM diagnosis codes from all hospitalizations in the 12 months preceding the index hospitalization. The

methods for deriving CC variables from administrative data have been extensively described elsewhere(1, 2). The CC derived variables included in the analysis has been previously shown to be a robust measure of patient risk status and to be superior to other methods in predicting mortality including AMI specific mortality.(3, 4) In this analysis, ICD9 diagnosis codes were cross-walked to matching ICD10AM diagnostic code for each CC and were only derived from inpatient data.

1B. Acute Complications

Acute complications were derived from secondary ICD10 diagnostic coding from the initial hospital of presentation during the index hospitalization (i.e. acute complication occurring prior to potential transfer). Acute complications included typical complications encountered during AMI presentations and are indicated below with the corresponding ICD10 coding. With the exception of CHF, the ICD10AM coding used to derive the acute complications represent acute complications only and are specifically excluded from assessment of background history derived from the CC model described above to present double counting. ICD10AM coding does not distinguish congestive heart failure (CHF) as acute or chronic.

Acute complication	**ICD10AM coding**
Mechanical Complication of AMI	123.0-123.8
Cardiogenic Shock	R57.0
Cardiac Arrest	I46.0, I46.1, I46.9,
Ventricular arrhythmia	VT (I47.2), Vfib/flutter (I49.0)
Acute renal failure	N17.0-N17.2,N17.8, N17.9
Ischemic Stroke	I63.0-I63.9
Major Bleeding (all cause)	Multiple codes to identify all cause bleeding derived from 1CD10AM equivalent of ICD9 diagnostic codes previously published in the literature to identify major bleeding(5) I85.0, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2 K27.4, K27.6, K28.0, K28.4,

	K28.6, K29.0, K62.5, K66.1, K92.0, K92.1, K92.2, I60.0, I60.1 I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62.0, I62.1, I62.9, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, R31, R31.0, R31.1, R31.8, R04.0, R04.1, R04.2, R04.8, R04.9, R58, T81.0
Congestive Heart Failure	I50.0, I50.1 and I50.9

1C. Covariate balance pre and post propensity score matching (all variables)

Supplementary Table 1: Baseline Characteristics (All Variables)

	Unadjusted data			PS matched cohort		
	Transfer	**Non- Transfer**	**P Value**	**Transfer**	**Non-Transfer**	**P Value**
	N=10107	N=30375		N=8427	N=8427	
Age (median± SD)	65.1±12.9	70.8±14.1	<0.01	66.9±12.5	67.3±14.6	0.06
% Male	7129 (70.5)	18809 (61.9)	<0.01	5684 (67.5)	5634 (66.9)	0.41
Private insurance	2599 (25.7)	6406 (21.1)		1969 (23.4)	1995 (23.7)	0.64
Year of presentation						
- 2004	1140 (11.3)	4630 (15.2)	<0.01	1030 (12.3)	1023 (12.1)	0.99
- 2005	2181 (21.6)	7372 (24.3)		1868 (22.2)	1854 (22.0)	
- 2006	2638 (26.1)	7211 (23.7)		2171 (25.8)	2157 (25.6)	
- 2007	2772 (27.4)	7580 (25.0)		2242 (26.6)	2267 (26.9)	
- 2008	1376 (13.6)	3582 (11.8)		1116 (13.2)	1126 (13.4)	
Principle diagnosis at index admission						
- STEMI	4175 (41.3)	10015 (33.0)	<0.01	3124 (37.1)	3037 (36.0)	0.16
- NSTEMI	5932 (58.7)	20360 (67.0)		5303 (62.9)	5390 (64.0)	
Cardiovascular history*						
PTCA (CC 199)	100 (1.0)	388 (1.3)	0.02	91 (1.1)	76 (0.9)	0.24
CABG (CC 200)	14 (0.14)	71 (0.23)	0.07	13 (0.2)	15 (0.2)	0.71
Heart failure (CC 80)	1026 (10.2)	6379 (21.0)	<0.01	239 (2.8)	267 (3.2)	0.21

AMI (CC 81)	1378 (13.6)	4626 (15.2)	<0.01	119 (1.4)	145 (1.7)	0.11
Unstable angina (CC 82)	2044 (20.2)	7374 (24.3)	<0.01	394 (4.7)	427 (5.1)	0.24
Chronic atherosclerosis (CC 83, 84)	5776 (57.2)	22254 (73.3)	<0.01	3216 (38.2)	3140 (37.3)	0.23
Cardiopulmonary-respiratory failure or shock (CC 79)	324 (3.2)	1538 (5.1)	<0.01	45 (0.5)	39 (0.5)	0.51
Valvular heart disease (CC 86)	439 (4.3)	2752 (9.1)	<0.01	263 (3.1)	324 (3.8)	0.01
Comorbidity*						
Hypertension (CC 89, 91)	6027 (59.6)	20013 (65.9)	<0.01	4412 (52.4)	4444 (52.7)	0.62
Stroke (CC 95, 96)	183 (0.5)	850 (2.8)	<0.01	38 (0.5)	38 (0.5)	1.00
Cerebrovascular disease (CC 97,98,99,103)	255 (2.5)	1211 (4.0)	<0.01	75 (0.9)	76(0.9)	0.93
Renal failure (CC 131)	693 (6.9)	3877 (12.8)	<0.01	149 (1.8)	153 (1.8)	0.82
COPD (CC 108)	666 (6.6)	3409 (11.2)	<0.01	439 (5.2)	449 (5.3)	0.73
Pneumonia (CC 111, 112, 113)	271 (2.7)	1596 (5.3)	<0.01	75 (0.9)	81 (1.0)	0.63
Diabetes (CC 15-20, 120)	1706 (16.9)	6328 (20.8)	<0.01	1134 (13.5)	1117 (13.3)	0.70
Protein-caloric malnutrition (CC 21)	55 (0.5)	351 (1.2)	<0.01	10 (0.1)	11 (0.1)	0.83
Dementia (CC 49-50)	207 (2.1)	2430 (8.0)	<0.01	86 (1.0)	111 (1.3)	0.07
Hemiplegia, paraplegia, paralysis, functional disability (CC 68,69,100-102, 177,178)	474 (4.7)	2417 (8.0)	<0.01	153 (1.8)	169 (2.0)	0.37
Peripheral vascular disease (CC 104, 105)	789 (7.8)	3342 (11.0)	<0.01	212 (2.5)	228 (2.7)	0.44
Metastatic cancer (CC 7,8)	214 (2.1)	1025 (3.4)	<0.01	58 (0.7)	71 (0.8)	0.26
Trauma (CC 154-156, 158-162)	641 (6.3)	3277 (10.8)	<0.01	230 (2.7)	266 (3.2)	0.10
Major psychiatric disorder (CC 54-56)	88 (0.9)	398 (1.3)	0.05	45 (0.5)	45 (0.5)	1.00
Chronic liver disease (CC 25-27)	84 (0.8)	349 (1.2)	0.01	43 (0.5)	42 (0.5)	0.91
HIV/AIDS (CC1)	54 (0.2)	7 (0.1)	0.01	9 (0.1)	7 (0.1)	0.62
Septicemia/Shock (CC2)	310 (1.0)	34 (0.3)	<0.01	30 (0.4)	33 (0.4)	0.70
Opportunistic infections (CC5)	93 (0.3)	7 (0.1)	<0.01	7 (0.1)	6 (0.1)	0.78
Lymphatic, head and neck, brain, and other major cancers (CC9)	206 (0.7)	31 (0.3)	<0.01	37 (0.4)	31 (0.4)	0.47
Breast, prostate, colorectal and other cancers and tumors (CC10)	697 (2.3)	145 (1.4)	<0.01	134 (1.6)	137 (1.6)	0.85
Intestinal obstruction/perforation	257 (0.9)	45 (0.5)	<0.01	45 (0.5)	44 (0.5)	0.92
Pancreatic disease (CC 32)	68 (0.2)	14 (0.1)	0.10	5 (0.1)	13 (0.2)	0.06
Inflammatory bowel disease (CC 33)	64 (0.2)	16 (0.2)	0.30	18 (0.2)	16 (0.2)	0.73
Bone/joint/muscle infections/necrosis (CC 37)	117 (0.4)	14 (0.1)	<0.01	11 (0.1)	14 (0.2)	0.55

Rheumatoid Arthritis, Inflammatory Connective Tissue Disease (CC 38)	349 (1.2)	76 (0.8)	<0.01	69 (0.8)	72 (0.9)	0.78
Severe Hematological Disorders (CC 44)	167 (0.6)	19 (0.2)	<0.01	18 (0.2)	19 (0.2)	0.87
Disorders of Immunity (CC 45)	38 (0.1)	4 (0.0)	0.02	4 (0.1)	4 (0.1)	1.00
Drug/Alcohol Psychosis (CC 51)	213 (0.7)	45 (0.5)	0.01	50 (0.6)	42 (0.5)	0.40
Drug/Alcohol Dependence (CC 52)	325 (1.1)	93 (0.9)	0.12	89 (1.1)	87 (1.0)	0.88
Schizophrenia (CC 54)	98 (0.3)	21 (0.2)	0.06	24 (0.3)	20 (0.2)	0.55
Major Depressive, Bipolar, and Paranoid Disorders (CCC 55)	154 (0.5)	28 (0.3)	<0.01	25 (0.3)	27 (0.3)	0.78
Polyneuropathy (CC 71)	407 (1.3)	72 (0.7)	<0.01	71 (0.8)	71 (0.8)	1.00
Multiple Sclerosis (CC 72)	20 (0.1)	8 (0.1)	0.66	8 (0.1)	8 (0.1)	1.00
Parkinson's and Huntington's Diseases (CC 73)	276 (0.9)	26 (0.3)	<0.01	25 (0.3)	26 (0.3)	0.89
Seizure Disorders and Convulsions (CC 74)	169 (0.6)	23 (0.2)	<0.01	24 (0.3)	23 (0.3)	0.88
Coma, Brain Compression/Anoxic Damage (CC 75)	166 (0.6)	11 (0.1)	<0.01	11 (0.1)	11 (0.1)	1.00
Respirator Dependence/Tracheostomy Status (CC 77)	32 (0.1)	3 (0.0)	0.03	7 (0.1)	3 (0.0)	0.20
Respiratory Arrest (CC 78)	45 (0.2)	7 (0.1)	0.06	9 (0.1)	6 (0.1)	0.44
Proliferative Diabetic Retinopathy and Vitreous Hemorrhage (CC 119)	13 (0.0)	3 (0.0)	0.56	2 (0.0)	3 (0.0)	1.00
Dialysis Status (CC 130)	242 (0.8)	34 (0.3)	<0.01	22 (0.3)	34 (0.4)	0.11
Nephritis (CC 132)	47 (0.2)	8 (0.1)	0.07	9 (0.1)	8 (0.1)	0.81
Specified Heart Arrhythmias (CC 92)	2256 (7.4)	325 (3.2)	<0.01	346 (4.1)	314 (3.7)	0.20
Decubitus Ulcer of Skin (CC 148)	226 (0.7)	20 (0.2)	<0.01	15 (0.2)	20 (0.2)	0.40
Chronic Ulcer of Skin, Except Decubitus (CC 149)	508 (1.7)	63 (0.6)	<0.01	76 (0.9)	62 (0.7)	0.23
Vertebral Fractures without Spinal Cord Injury (CC 157)	11 (0.0)	3 (0.0)	0.76	6 (0.1)	3 (0.0)	0.32
Major Complications of Medical Care and Trauma (CC 164)	1183 (3.9)	188 (1.9)	<0.01	176 (2.1)	184 (2.2)	0.67
Major Organ Transplant Status (CC 174)	36 (0.1)	12 (0.1)	1.00	11 (0.1)	11 (0.1)	1.00
Artificial Openings for Feeding or Elimination (CC 176)	258 (0.9)	45 (0.5)	<0.01	40 (0.5)	42 (0.5)	0.82
Acute Complications						
Mechanical Complication of AMI	8 (0.1)	61 (0.2)	0.01	8 (0.1)	9 (0.1)	0.81
Cardiogenic Shock	74 (0.7)	611 (2.0)	<0.01	71 (0.8)	76 (0.9)	0.68
Cardiac Arrest	138 (1.4)	800 (2.6)	<0.01	124 (1.5)	116 (1.4)	0.60
Ventricular Arrhythmia(VT/VF)	234 (2.3)	976 (3.2)	<0.01	194 (2.3)	197 (2.3)	0.88
Acute Renal Failure	144 (1.4)	1658 (5.5)	<0.01	143 (1.7)	154 (1.8)	0.52

Ischemic Stroke	10 (0.1)	192 (0.6)	<0.01	10 (0.1)	10 (0.1)	1.00
Major Bleeding	157 (1.6)	1318 (4.3)	<0.01	156 (1.9)	168 (2.0)	0.50
Heart Failure	739 (7.3)	5439 (17.9)	<0.01	731 (8.7)	736(8.7)	0.89
Presenting Hospital Characteristics						
Hospital region						
- Major city area	6746 (66.8)	23934 (78.8)	<0.01	5459 (64.8)	5489 (65.1)	0.69
- Regional hospital	3361 (33.3)	6441 (21.2)	<0.01	2968 (35.2)	2938 (35.9)	
Hospital Peer Group						
- Principle referral	5783 (57.2)	21539 (70.9)	<0.01	4946 (58.7)	4953 (58.8)	0.32
- Large hospital	2799 (27.7)	4235 (14.5)		2115 (25.1)	2171 (25.8)	
- Medium hospital	826 (8.2)	1970 (6.5)		784 (9.3)	735(8.7)	
- Small acute hospital	340 (3.4)	373 (1.2)		229 (2.7)	248 (2.9)	
- Private hospital	359 (3.6)	2258 (7.4)		353 (4.2)	320 (3.2)	
Revascularization capable (PCI and/or CABG)	2269 (22.5)	17966 (59.2)	<0.01	2260 (26.8)	2181 (25.9)	0.17

Abbreviations are as described within the manuscript text.

2. Subgroup analysis of the effect of inter-hospital transfer on long-term mortality stratified by the type of AMI (STEMI vs NSTEMI)

		STEMI*				NSTEMI*			
Subgroup		**IHT**	**No IHT**	**OR**	**95%CI**	**IHT**	**No IHT**	**OR**	**95%CI**
Age	<65	80/1395	109/1398	0.73	0.54-0.97	111/2263	137/2326	0.83	0.68-1.07
	≥65	371/1547	577/1544	0.59	0.58-0.67	706/3232	1093/3169	0.57	0.52-0.63
Region	Major City	272/1656	384/1677	0.68	0.59-0.80	592/3850	900/3791	0.61	0.55-0.68
	Regional Hospital	179/1286	302/1265	0.56	0.46-0.67	225/1645	330/1704	0.68	0.57-0.80
Revascularization capable hospitals		116/788	121/759	0.90	0.70-1.16	219/1466	268/1439	0.79	0.66-0.95
Non-Revascularization hospitals		335/2154	565/2183	0.57	0.50-0.65	598/4029	962/4056	0.59	0.53-0.65
Public hospitals only		435/2775	652/2762	0.63	0.56-0.71	801/5316	1198/5296	0.63	0.58-0.69
Excluding in-hospital deaths		305/2796	406/2662	0.70	0.61-0.82	727/5405	1105/5370	0.62	0.57-0.68
By risk quartile at presentation									
	Quartile 1 (lowest risk)	27/689	37/782	0.82	0.50-1.34	58/1262	76/1485	0.91	0.65-1.28
	Quartile 2	54/796	58/675	0.80	0.55-1.15	66/1465	96/1283	0.61	0.44-0.82
	Quartile 3	124/784	124/687	0.88	0.69-1.13	229/1513	248/1235	0.72	0.60-0.86
	Quartile 4 (highest risk)	246/673	467/798	0.53	0.45-0.61	464/1255	810/1492	0.58	0.51-0.64

*STEMI cohort included 5,884 patients and NSTEMI cohort included 10,990 patients. Each propensity score matched cohort included an equal proportion of transferred and non-transferred patients.

3. Inverse probability treatment weighted (IPTW) propensity analysis

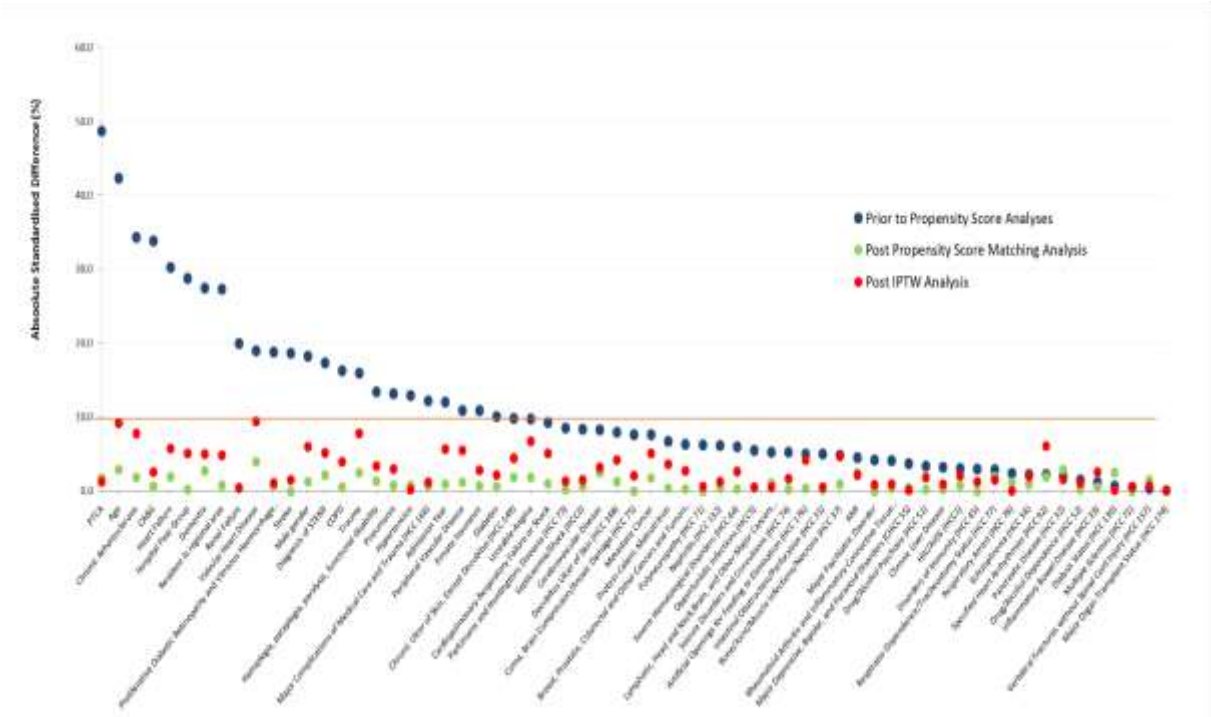
3A. Method

Propensity score matching allows the most robust estimation of the average treatment effect for the treated (ATT), i.e. the effect on mortality for those who were transferred.(6) However, matching excludes a significant proportion of the population who are unmatched. To evaluate whether the survival benefit of IHT evident in the PSM cohort is applicable to the entire population, we conducted an Inverse Probability Treatment Weighted (IPTW) propensity score analysis. For this analysis morality was adjusted for baseline covariates by weighting the analysis using IPTWs derived from the propensity score. IPTW method allow estimation of the average effect of treatment in the entire study population, i.e. the expected effect on mortality for the entire population if the entire population was assumed to have received IHT.(6) Adequacy of the IPTW propensity score model was assessed by comparing covariate balance before and after IPTW adjustment using standardized differences.

3B. Covariate balance post IPTW PS analysis

Covariate Balance post IPTW analysis is indicated in figure below. Median standardized difference post IPTW analysis was 2.20 (IQR 1.13-4.51) indicating a significant improvement in covariate balance from baseline (median standardized difference 8.31, IQR 4.2-16.0) but slightly inferior to covariate balance following propensity score matching (median standardized difference 0.74, IQR 0.28-1.42). Irrespective, all covariates were at or below 10, the general accepted threshold below which covariate imbalance is considered insignificant.(6)

Figure: Covariate balance between transferred and non-transferred cohorts for individual covariates (as measured by the absolute standardised difference) prior to propensity score analyses and following propensity score matching and IPTW analyses respectively. The figure shows that both propensity score methods achieve good covariate balance (as indicated by a standardised difference <10 for all covariates [red line]). However, propensity score matching (green dots) achieved a slightly superior covariate balance compared with the IPTW method (red dots) as indicated by a lower standardised difference for most covariates.



3C. Comparison of mortality following IPTW adjusted analysis

Mortality	Unadjusted Point Estimate† (95%CI)	PSM cohort Point Estimate† (95%CI)	IPTW adjusted Point Estimate† (95%CI)
In-hospital Mortality	0.37 (0.33-0.42)	0.67 (0.57- 0.79)	0.69 (0.61-0.77)
30 day	0.35 (0.31-0.40)	0.60 (0.52-0.70)	0.65 (0.59-0.71)
1 year	0.34 (0.31-0.37)	0.58 (0.52-0.64)	0.67 (0.62-0.71)
Long-term Mortality#	0.40 (0.38-0.42)	0.65 (0.61-0.70)	0.76 (0.74-0.79)

† Point estimate given are Relative Risk (RR) for revascularization and in-hospital mortality. Point estimate shown for 30 day, 1 year and long-term mortality are Hazard Ratios (HR). In both cases the non-transfer group is referent group

Mean follow-up time 3.5 years (min 1.5 years, max 5.5 years).

4. Supplemental Figures

Figure S1: The distribution of the Propensity Score by the actual transfer status.

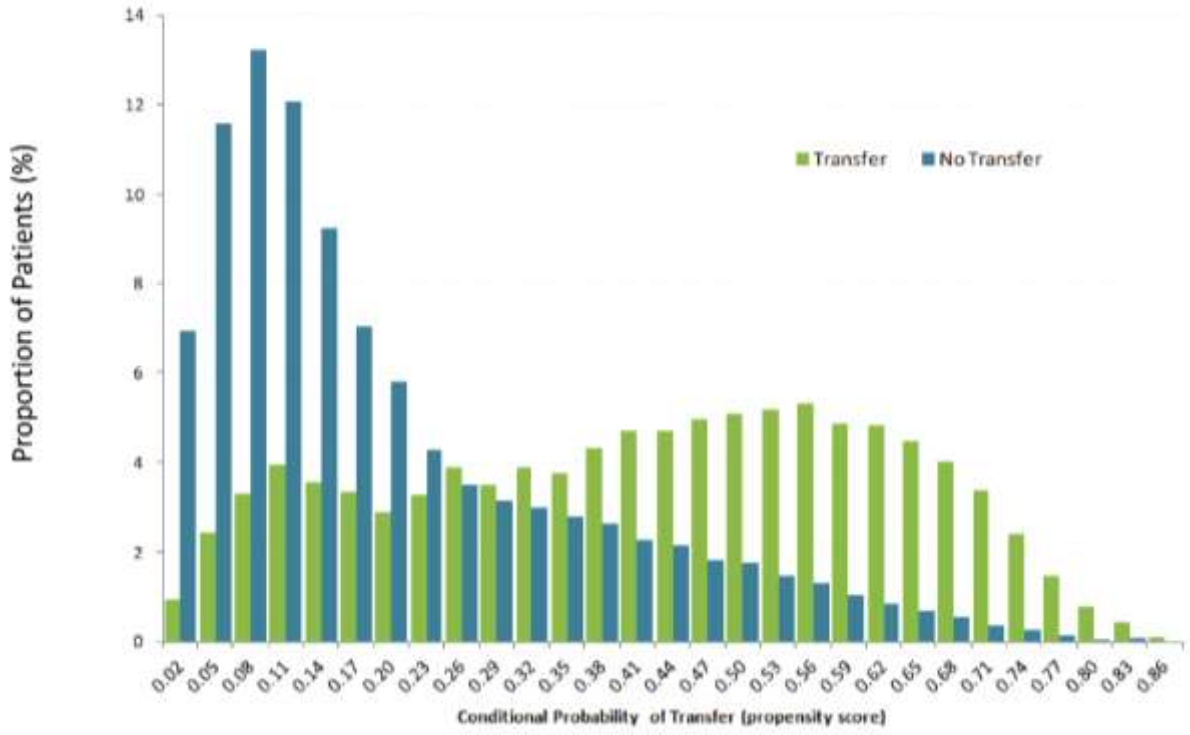


Figure S2: Subgroup analysis of 30-day mortality between transferred and non-transferred patients.†P for statistical interaction with IHT, *No interaction term calculated as in-hospital death directly affects 30-day mortality.

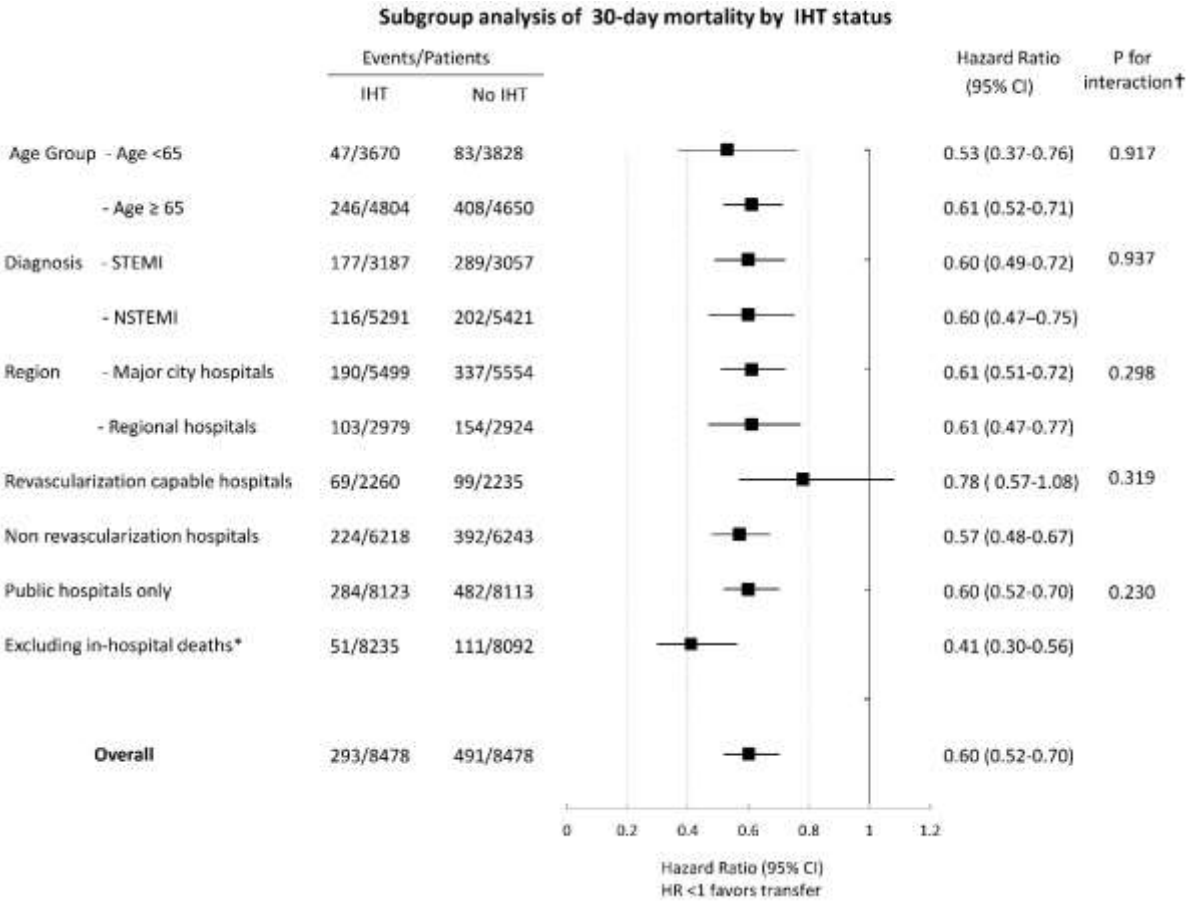
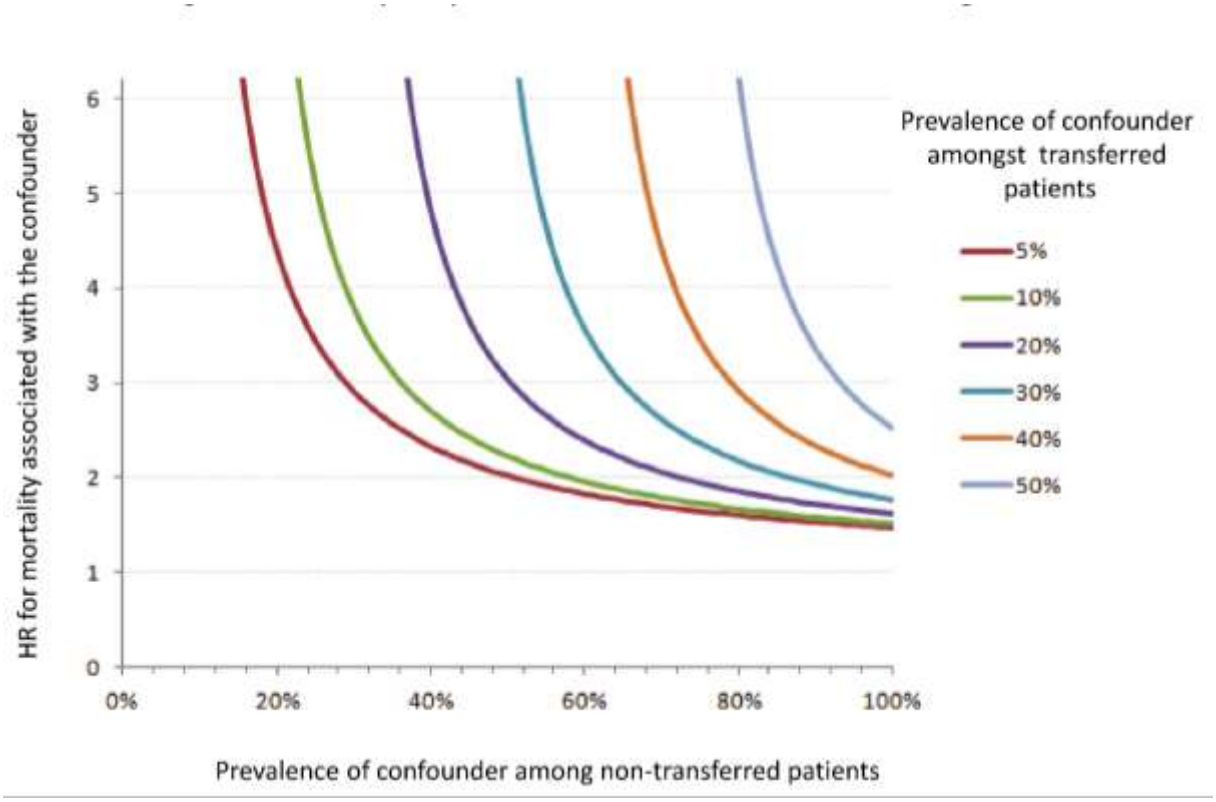


Figure S3: A sensitivity analysis of the potential for a single unmeasured binary confounder to explain the observed hazard ratio (HR) for long-term mortality. It shows the complex relationship required for a confounder to shift the upper 95% confidence interval of the overall treatment effect estimate from 0.70 to 1.00. For example, if an unmeasured baseline confounder were present in 10% of the patients who were transferred (green curved line) then the prevalence of the confounder in the non-transferred population has to be at least 25% and have a HR of 6.0 for mortality. If the prevalence of such a confounder were 40% or 60% in the non-transferred group then the hazard ratios that would be required for an unmeasured confounder to account for the observed lower mortality with transfer would be 2.32, and 1.82, respectively. An unmeasured confounder also has to occur prior to transfer and be independent of all other measured variables.



5. Supplementary appendix references

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