SUPPLEMENTAL MATERIAL

Illness trajectories after revascularization in patients with peripheral artery disease (PAD): A unified approach to understanding the risk of major amputation and death

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Appendix A: Flexible parametric proportional hazards model

Three transition intensities are defined for the Markov illness-death model:

(1) transition hazard $h_1(t)$, from revascularization to major amputation;
(2) transition hazard $h_2(t)$, from revascularization to death without major amputation;
(3) transition hazard $h_3(t)$, from major amputation to death.

Define cumulative hazard function as $H_k(t)=\int_0^t h_k(s)ds$, where k=1,2,3. The time scale t is defined as time from the index revascularization.

The flexible parametric models are on the log cumulative hazard scale, and restricted cubic splines are used to estimate the cumulative baseline hazard functions. The flexible parametric proportional hazards model can be written as,

$$\begin{aligned}\ln\{H_k(t|x_i)\} &= \ln\{H_{0k}(t)\} + x_i^T\beta \\ &= \gamma_0 + \gamma_1 \ln(t) + \gamma_2 v_1(\ln(t)) + \cdots + \gamma_{m+1} v_m(\ln(t)) + x_i^T\beta\end{aligned}$$

where $H_{0k}(t)$ is the cumulative baseline hazard function of transition hazard $h_k(t)$, the j^{th} basis function is defined for j=1,…m as

$$v_j(\ln(t)) = \left(\ln(t) - K_j\right)_+^3 - \phi_j(\ln(t) - K_{min})_+^3 - (1-\phi_j)(\ln(t) - K_{max})_+^3$$

and,

$$\phi_j = \frac{K_{max} - K_j}{K_{max} - K_{min}}$$
$$(\ln(t) - a)_+ = \max(0, \ln(t) - a)$$

The points K_{min}, K_1,…,K_m, K_{max} are called knots, and K_{min} and K_{max} are the minimum and maximum observed event times, respectively. The Bayesian information criterion (BIC) is used to select the number of knots (i.e., the number of degree freedom) for the hazards models.

Covariates x_i represents patient and clinical characteristics at revascularization, include: *age, sex, deprivation quintile, Diabetes mellitus, RCS Charlson score, Frailty index, admission type, PAD indicator, procedure distal localization and procedure type*.

Table S1. ICD-10 diagnosis codes and OPCS codes for lower limb procedures

Condition	**ICD-10 Codes**
Diabetes	E10x, E11x, E12x, E13x, E14x
Peripheral circulatory complications of diabetes	E10.5, E11.5, E13.5, E14.5
Peripheral artery disease	I70, I73, I77
Osteomyelitis	M86x
Ulcer	L89x, L984, L97x
Gangrene	R02x
Lower limb Procedure	**OPCS-4.8 Codes**
Open surgical revascularization	L161, L162, L163, L168, L169, L206, L216, L501, L502, L503, L504, L505, L506, L511, L512, L513, L514, L515, L516, L518, L519, L521, L522, L528, L529**,** L581, L582, L583, L584, L585, L586, L587, L588, L589, L591, L592, L593, L594, L595, L596, L597, L598, L599, L601, L602, L603, L604, L608, L609, L651, L652, L653, L658, L659, L681, L682, L683, L684, L688, L689,
Endovascular revascularization	L541, L544, L548, L549, L631, L635, L638, L639, L662, L665, L667, L668, L669, L711, L718, L719
Lower limb major amputation	X09

Table S2. Unadjusted predicted probabilities (%) and 95% confidence intervals for patients at four states from the index revascularization, by admission mode. Amputation refers to major amputation.

	Alive without amputation	Alive with amputation	Dead after amputation	Dead without amputation
Elective patients (n=61 783)				
6 months	94.4 (93.9-94.9)	1.7 (1.4-1.9)	0.3 (0.2-0.4)	3.7 (3.3-4.1)
1 year	90.4 (89.7-91.0)	2.1 (1.8-2.4)	0.6 (0.4-0.7)	6.9 (6.4-7.5)
2 years	83.3 (82.6-84.1)	2.6 (2.3-2.9)	1.1 (0.9-1.3)	13.0 (12.4-13.6)
3 years	76.9 (76.0-77.8)	2.8 (2.4-3.1)	1.6 (1.3-1.9)	18.7 (18.0-19.5)
4 years	70.6 (69.6-71.5)	2.8 (2.4-3.1)	2.1 (1.8-2.5)	24.5 (23.6-25.5)
5 years	64.3 (63.3-65.4)	2.6 (2.3-3.0)	2.7 (2.4-3.1)	30.3 (29.3-31.3)
Non-elective patients (n=32 907)				
6 months	69.5 (68.4-70.6)	10.4 (9.8-11.1)	2.6 (2.2-3.0)	17.5 (16.6-18.4)
1 year	61.0 (59.9-62.2)	11.0 (10.3-11.7)	4.2 (3.7-4.6)	23.8 (22.8-24.7)
2 years	50.0 (48.9-51.1)	10.8 (10.1-11.5)	6.5 (6.0-7.0)	32.7 (31.7-33.7)
3 years	41.2 (40.1-42.4)	9.8 (9.2-10.5)	8.7 (8.1-9.3)	40.2 (39.1-41.3)
4 years	34.1 (33.0-35.2)	8.6 (7.9-9.2)	10.8 (10.1-11.4)	46.6 (45.5-47.7)
5 years	28.3 (27.3-29.3)	7.4 (6.7-8.0)	12.5 (11.8-13.2)	51.8 (50.7-53.0)

Table S3. Adjusted hazard ratios (aHR) from multivariable regressions using flexible parametric proportional hazards models for three transition processes

	Transit 1: Revasc - Amp		Transit 2: Revasc - death		Transit 3: Amp - death	
	aHR (95% CI)	p value	aHR (95% CI)	p value	aHR (95% CI)	p value
Age (years)		<0.001		<0.001		<0.001
50-54	1.23 (1.12-1.35)		0.37 (0.34-0.40)		0.61 (0.53-0.70)	
55-59	1.09 (1.01-1.19)		0.49 (0.47-0.53)		0.64 (0.57-0.72)	
60-64	1.06 (0.99-1.14)		0.59 (0.56-0.62)		0.81 (0.73-0.90)	
65-69	1.07 (0.99-1.14)		0.79 (0.76-0.82)		0.82 (0.75-0.91)	
70-74	1		1		1	
75-79	0.92 (0.85-0.98)		1.32 (1.27-1.37)		1.03 (0.94-1.13)	
80-84	0.84 (0.78-0.91)		1.77 (1.70-1.84)		1.34 (1.22-1.47)	
85-89	0.61 (0.55-0.67)		2.42 (2.33-2.52)		1.64 (1.46-1.83)	
90+	0.47 (0.40-0.55)		3.42 (3.26-3.60)		1.90 (1.59-2.27)	
Sex		<0.001		<0.001		0.414
Female	1		1		1	
Male	1.18 (1.13-1.24)		1.10 (1.08-1.13)		1.03 (0.97-1.09)	
Deprivation quintile		<0.001		<0.001		0.149
Q1 (least deprived)	1		1		1	
Q2	1.04 (0.96-1.12)		1.01 (0.98-1.05)		1.04 (0.94-1.14)	
Q3	1.08 (1.00-1.16)		1.04 (1.01-1.08)		1.03 (0.94-1.14)	
Q4	1.17 (1.09-1.25)		1.08 (1.04-1.12)		1.00 (0.91-1.10)	
Q5 (most deprived)	1.25 (1.17-1.34)		1.11 (1.07-1.15)		1.10 (1.00-1.20)	
Diabetes mellitus		<0.001		<0.001		<0.001
No	1		1		1	
Yes	1.24 (1.19-1.30)		1.13 (1.10-1.16)		1.18 (1.11-1.25)	
RCS Charlson score		0.005		<0.001		<0.001
0	1		1		1	
1	1.07 (1.02-1.13)		1.27 (1.23-1.31)		1.32 (1.22-1.42)	
2	1.10 (1.03-1.18)		1.62 (1.57-1.68)		1.57 (1.44-1.71)	
3+	1.12 (1.04-1.20)		2.28 (2.20-2.37)		2.20 (2.00-2.42)	
Scarf frailty index		<0.001		<0.001		<0.001
Mild	1				1	
Moderate	1.57 (1.46-1.69)		1.29 (1.24-1.34)		1.05 (0.94-1.18)	
Severe	2.11 (1.94-2.29)		1.89 (1.82-1.97)		1.31 (1.16-1.48)	
Admission type		<0.001		<0.001		0.436
Elective	1		1		1	
Non-elective	3.07 (2.92-3.22)		1.63 (1.59-1.67)		0.98 (0.92-1.04)	
PAD indicator		<0.001		<0.001		0.318
No record of tissue loss	1		1		1	
With record of tissue loss	1.54 (1.47-1.61)		1.36 (1.32-1.39)		1.03 (0.97-1.09)	
Procedure most distal localization		<0.001		0.847		<0.001
Illiac	0.71 (0.66-0.77)		1.01 (0.98-1.04)		0.95 (0.86-1.05)	
Femoral	1		1		1	
Popliteal	1.27 (1.21-1.34)		0.99 (0.96-1.02)		0.88 (0.82-0.95)	
Crural	1.43 (1.36-1.51)		0.99 (0.96-1.03)		0.81 (0.76-0.87)	
Procedure type		<0.001		<0.001		<0.001
Endovascular	1		1		1	
Open	1.29 (1.23-1.36)		0.97 (0.94-1.00)		0.88 (0.82-0.94)	
Hybrid	1.11 (1.01-1.21)		1.08 (1.03-1.13)		0.90 (0.80-1.01)	

Table S4. Adjusted cumulative risks (95% CI) of major amputation and mortality (without major amputation) after the index revascularization for elective and non-elective patients, corresponding to estimates presented in Figure 3.

Time from revascularization	Major amputation % (95% CI)				Death without major amputation % (95% CI)			
	Aged 50-54	Aged 60-64	Aged 70-74	Aged 80-84	Aged 50-54	Aged 60-64	Aged 70-74	Aged 80-84
Elective patients								
1 year	6.3 (5.4-7.3)	5.4 (4.7-6.1)	5.1 (4.4-5.7)	4.2 (3.6-4.8)	2.9 (2.5-3.4)	4.7 (4.2-5.2)	7.8 (7.1-8.5)	13.5 (12.5-14.4)
2 years	7.8 (6.7-8.9)	6.7 (5.8-7.5)	6.2 (5.4-7.0)	5.1 (4.4-5.8)	5.0 (4.4-5.7)	8.0 (7.3-8.7)	13.2 (12.3-14.2)	22.2 (20.9-23.5)
3 years	9.0 (7.7-10.2)	7.6 (6.7-8.5)	7.0 (6.1-7.9)	5.7 (4.9-6.5)	7.3 (6.4-8.3)	11.6 (10.7-12.5)	18.8 (17.6-20.0)	30.9 (29.3-32.4)
4 years	9.9 (8.6-11.3)	8.5 (7.5-9.4)	7.7 (6.8-8.6)	6.2 (5.3-7.0)	9.9 (8.7-11.1)	15.5 (14.4-16.6)	24.8 (23.4-26.2)	39.7 (38.0-41.5)
5 years	10.8 (9.4-12.2)	9.2 (8.1-10.2)	8.3 (7.3-9.3)	6.5 (5.7-7.4)	12.9 (11.5-14.3)	20.0 (18.6-21.3)	31.4 (29.8-32.9)	48.7 (46.8-50.6)
Non-elective patients								
1 year	18.0 (16.0-20.0)	15.5 (14.1-17.0)	14.4 (13.1-15.7)	11.9 (10.6-13.2)	4.3 (3.7-4.9)	7.0 (6.3-7.6)	11.6 (10.7-12.4)	19.7 (18.5-21.0)
2 years	21.8 (19.5-24.1)	18.8 (17.1-20.4)	17.3 (15.9-18.7)	14.0 (12.6-15.5)	7.2 (6.3-8.1)	11.5 (10.6-12.5)	18.7 (17.5-20.0)	31.1 (29.5-32.7)
3 years	24.5 (22.1-27)	21.1 (19.3-22.9)	19.2 (17.7-20.8)	15.4 (13.8-16.9)	10.2 (9.0-11.3)	16.1 (14.9-17.3)	25.7 (24.3-27.1)	41.2 (39.3-43.1)
4 years	26.9 (24.2-29.6)	23.0 (21.0-24.9)	20.8 (19.1-22.4)	16.4 (14.7-18.0)	13.4 (12.0-14.8)	21.0 (19.5-22.4)	32.7 (31.1-34.4)	50.6 (48.6-52.6)
5 years	28.8 (26.0-31.7)	24.5 (22.5-26.5)	21.9 (20.2-23.6)	17.0 (15.4-18.7)	16.9 (15.1-18.6)	26.2 (24.6-27.8)	39.8 (38-41.6)	58.9 (56.9-60.9)

Figure S1 (a). Cumulative incidence of major amputation and mortality (without major amputation) after the index revascularization for elective and non-elective patients, comparison shown between diabetes statuses. Values of the remaining covariates were specified in Figure 3.

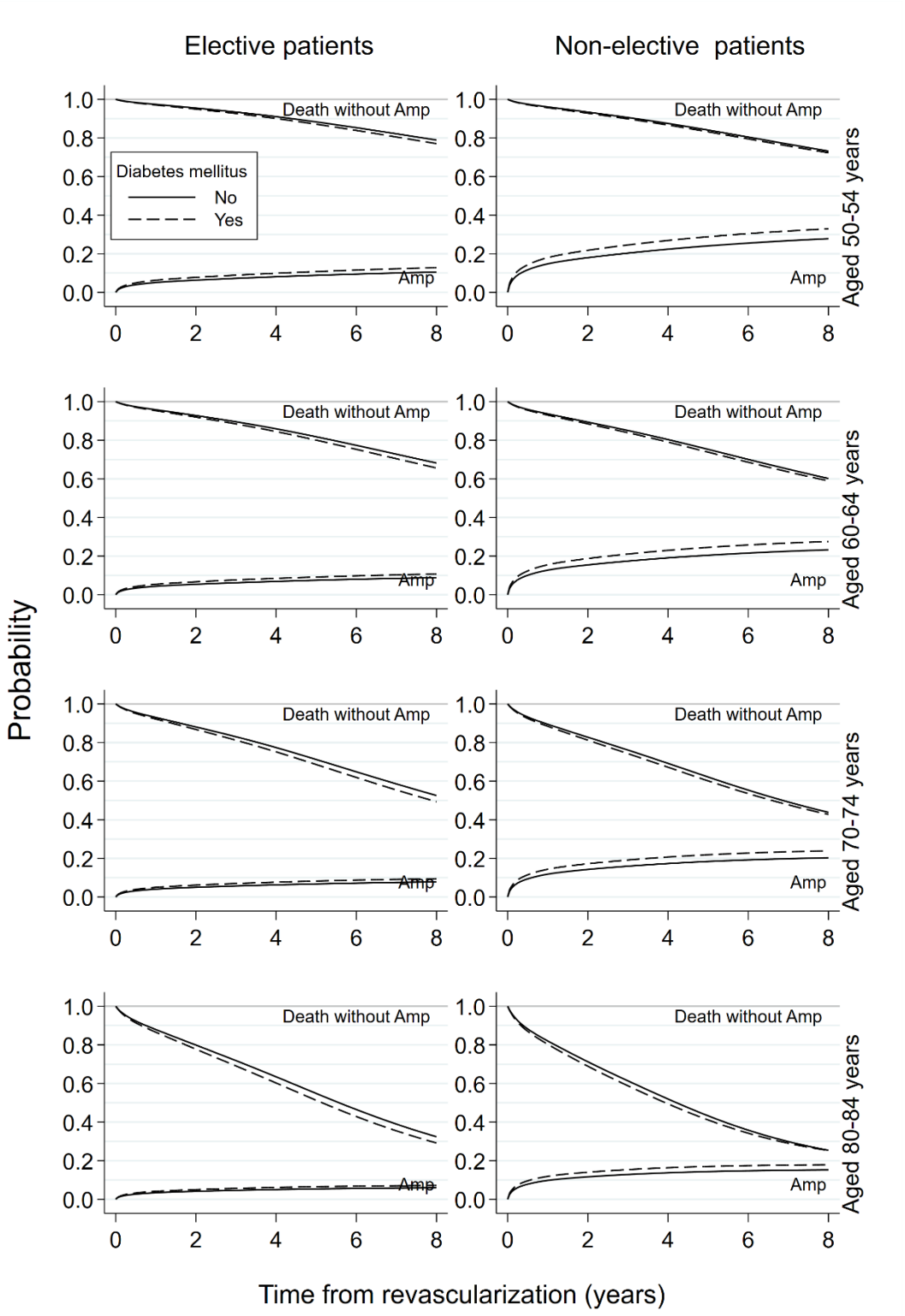


Figure S1 (b). Cumulative incidence of major amputation and mortality (without major amputation) after the index revascularization for elective and non-elective patients, comparison shown between the indications of tissue loss. Values of the remaining covariates were specified in Figure 3.

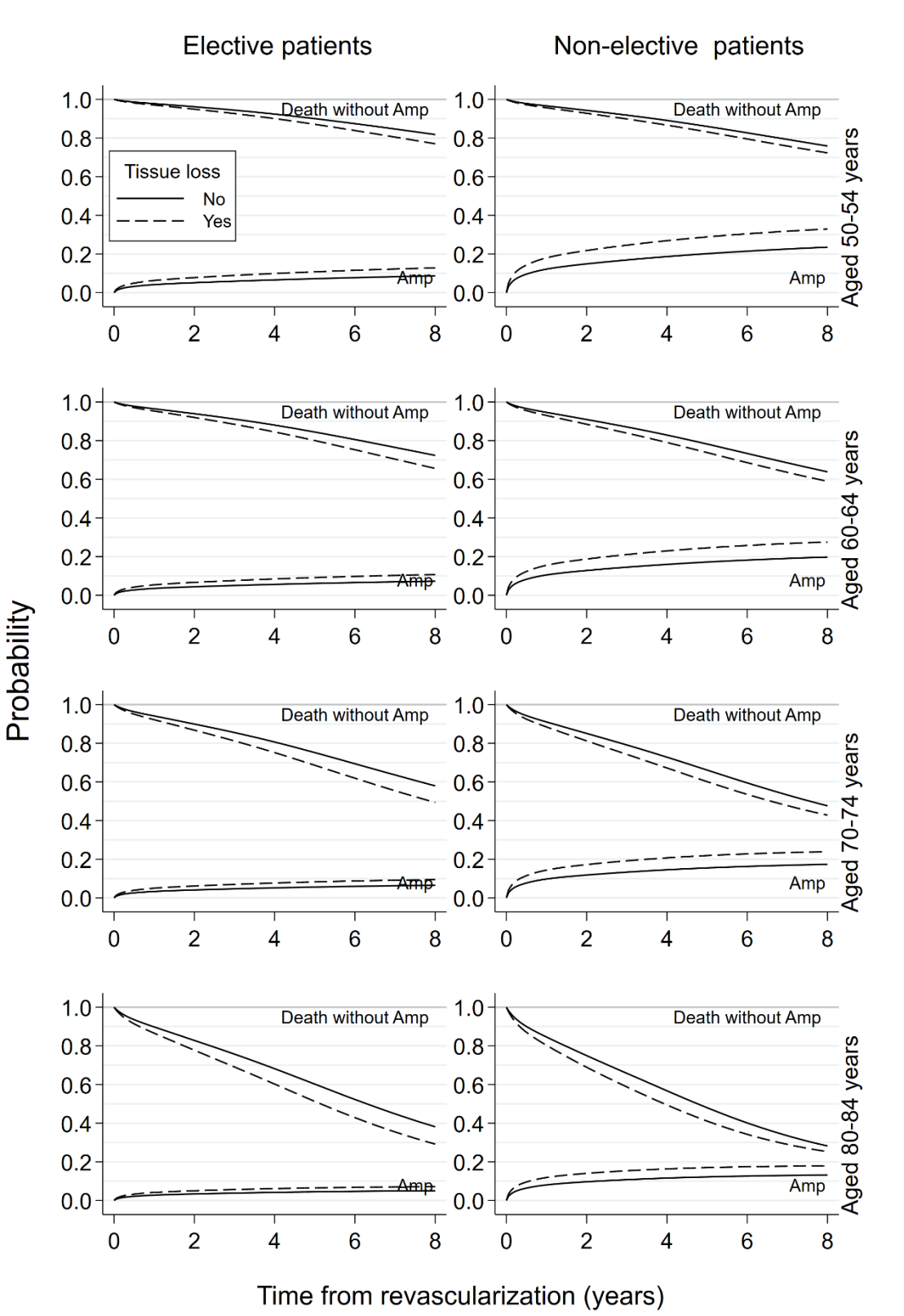


Figure S1 (c). Cumulative incidence of major amputation and mortality (without major amputation) after the index revascularization for elective and non-elective patients, comparison shown between patient frailty statuses. Values of the remaining covariates were specified in Figure 3.

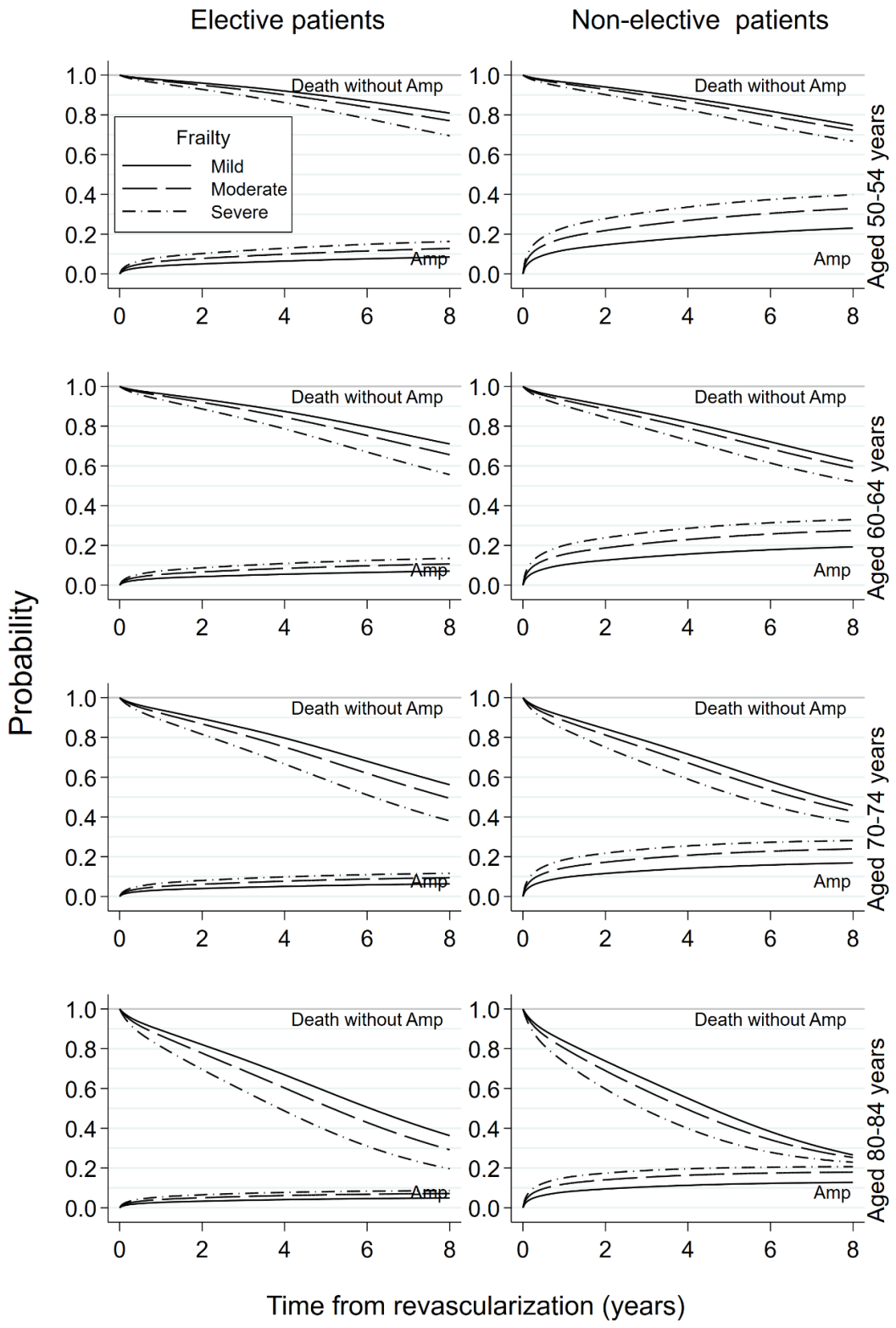


Figure S1 (d). Cumulative incidence of major amputation and mortality (without major amputation) after the index revascularization for elective and non-elective patients, comparison shown between RCS Charlson scores. Values of the remaining covariates were specified in Figure 3.

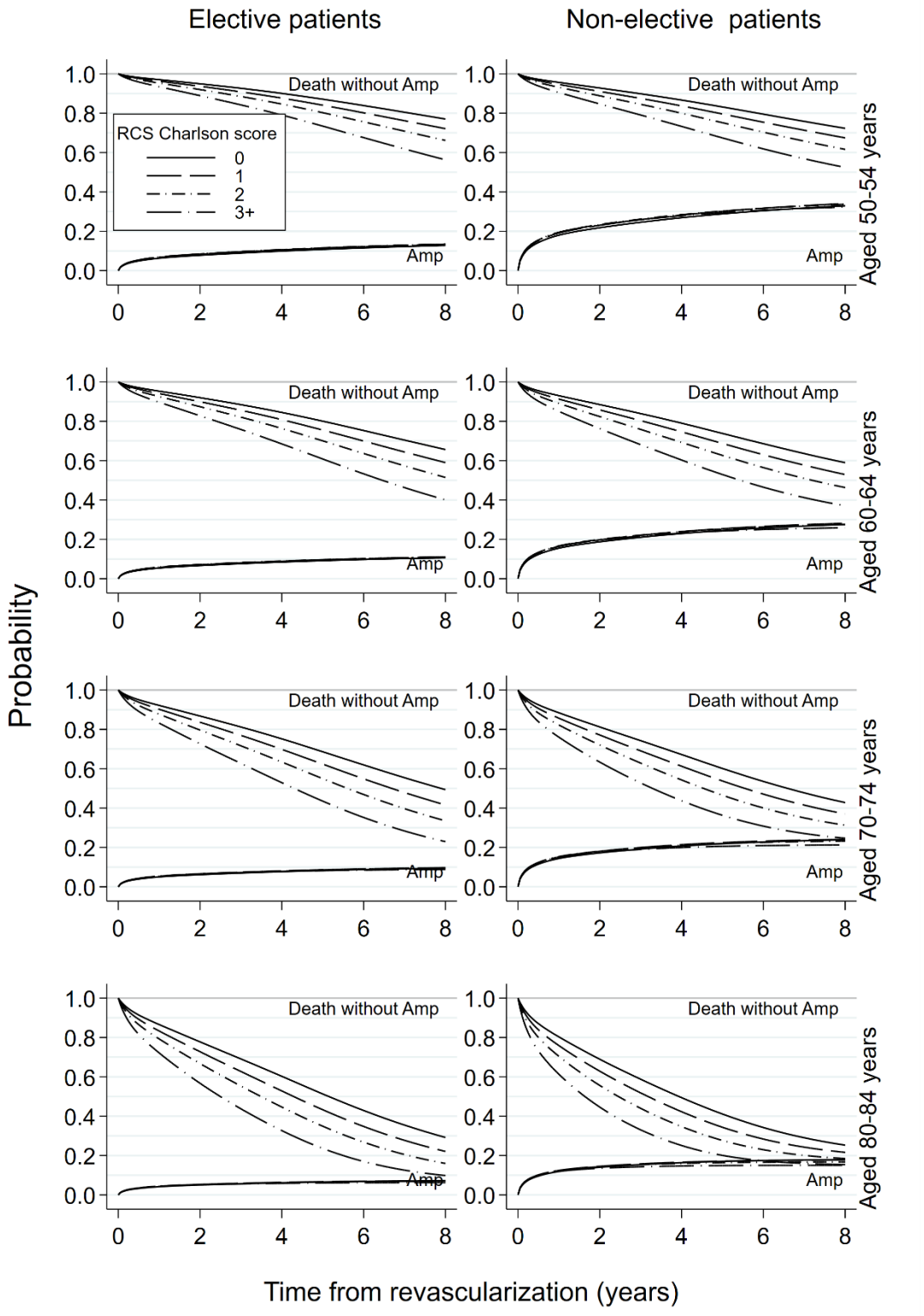


Figure S1 (e). Cumulative incidence of major amputation and mortality (without major amputation) after the index revascularization for elective and non-elective patients, comparison shown between the admission modes for the index revascularization. Values of the remaining covariates were specified in Figure 3.

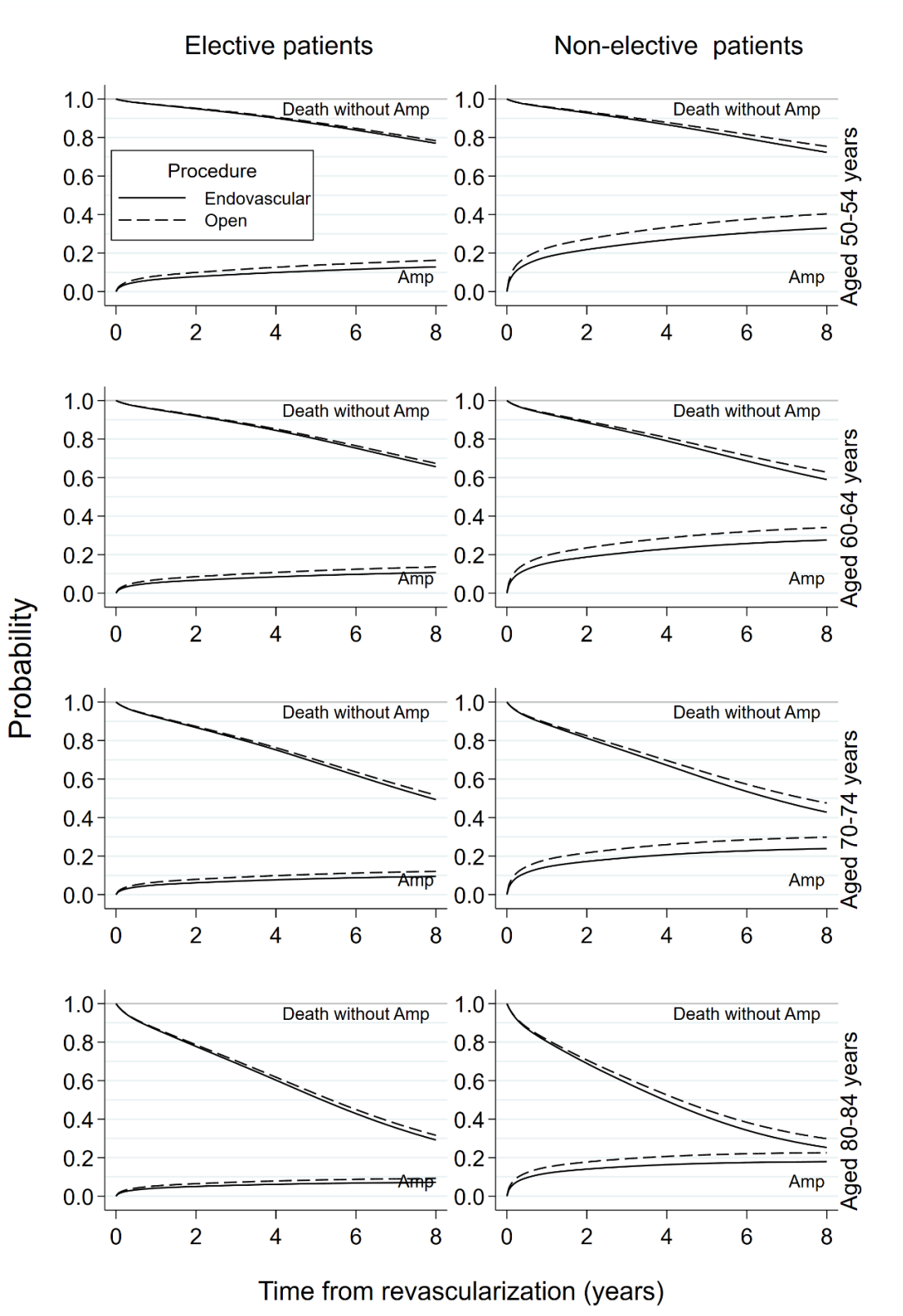


Figure S2. Dynamic risks of death after undergoing a major amputation, by age and RCS Charlson score. Each curve line represents the cumulative risk of death for the patient group who had major amputation at the specified time point from revascularization, e.g., red line represents those who had major amputation at 1 week from the index revascularization.

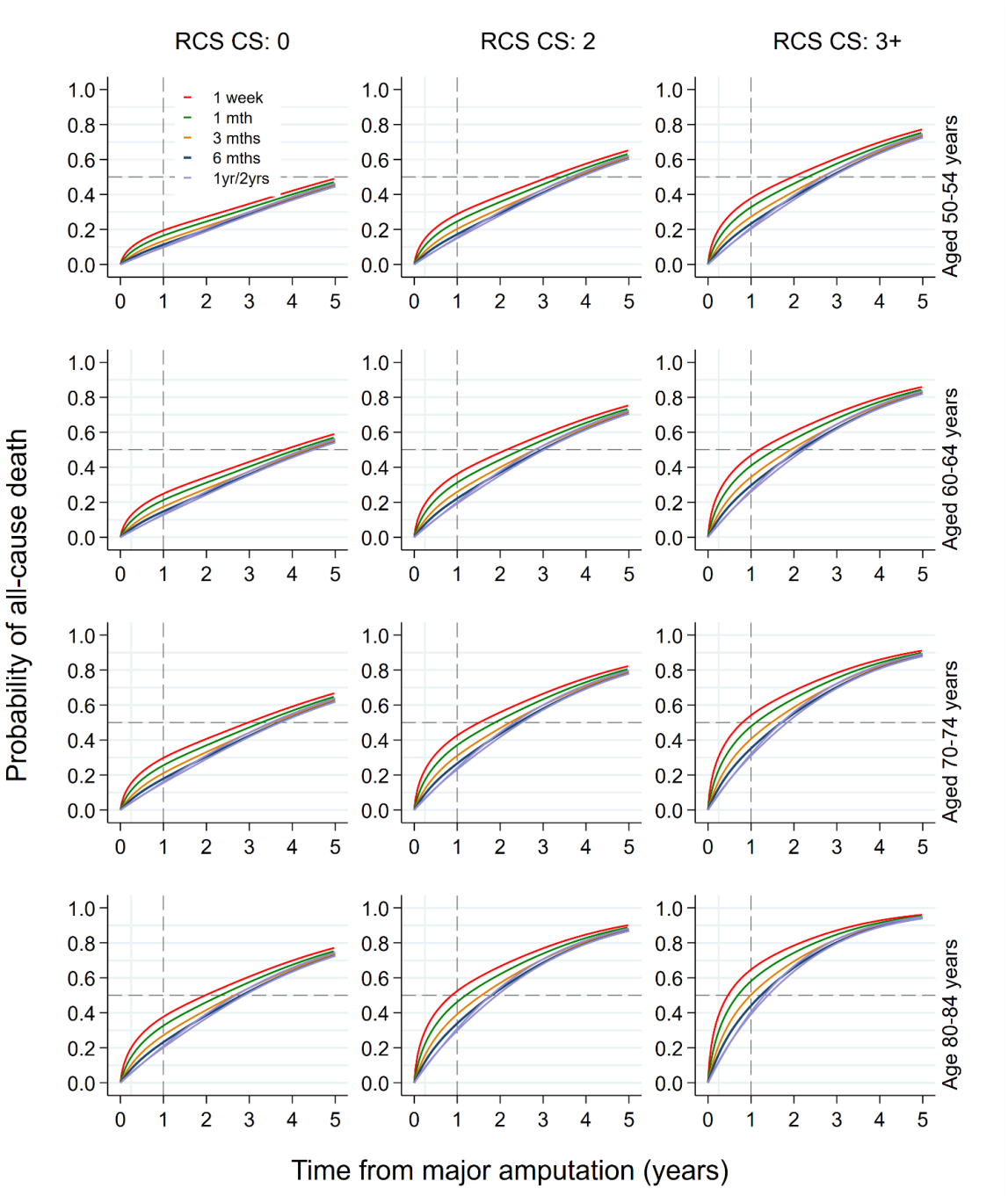


Figure S3. State occupation probabilities after the index revascularization for elective and non-elective patients. The light grey area represents cumulative incidence of death without major amputation; the dark grey area represents the probability of patients having died with major amputations, the orange area represents the probability of patients being alive with major amputations; the white area in the middle represents the probability of a patient remaining alive and without a major amputation. In producing these estimates, values of other covariates were: male, Q3 deprivation index, with diabetes, with a record of tissue loss, RCS Charlson score 0, moderate frailty, femoral procedure distal localization, and endovascular procedure.

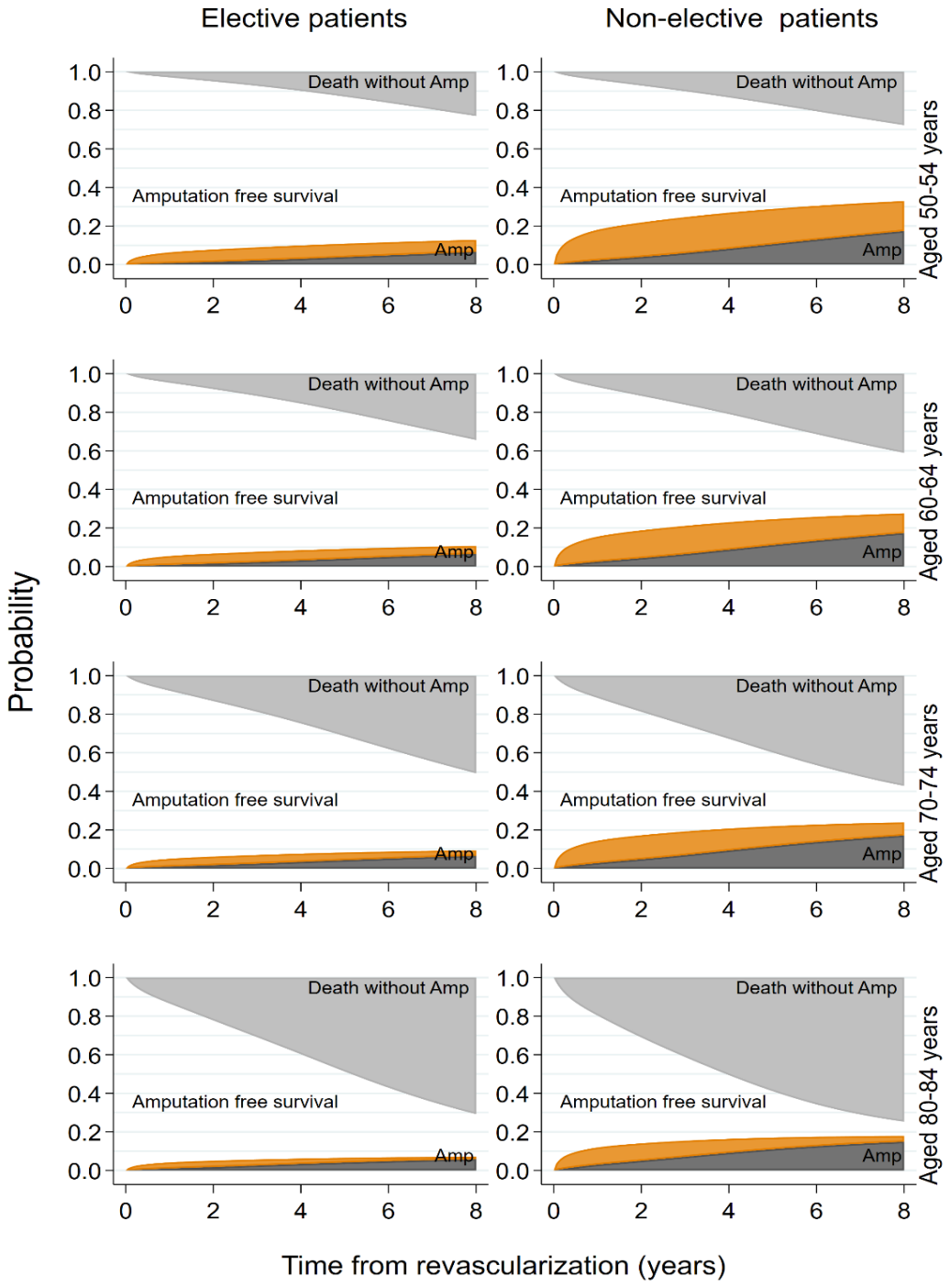


Figure S4 (a). Overall mortality after the index revascularization for elective and non-elective patients, comparison shown between diabetes statuses. Values of the remaining covariates were specified in Figure 3.

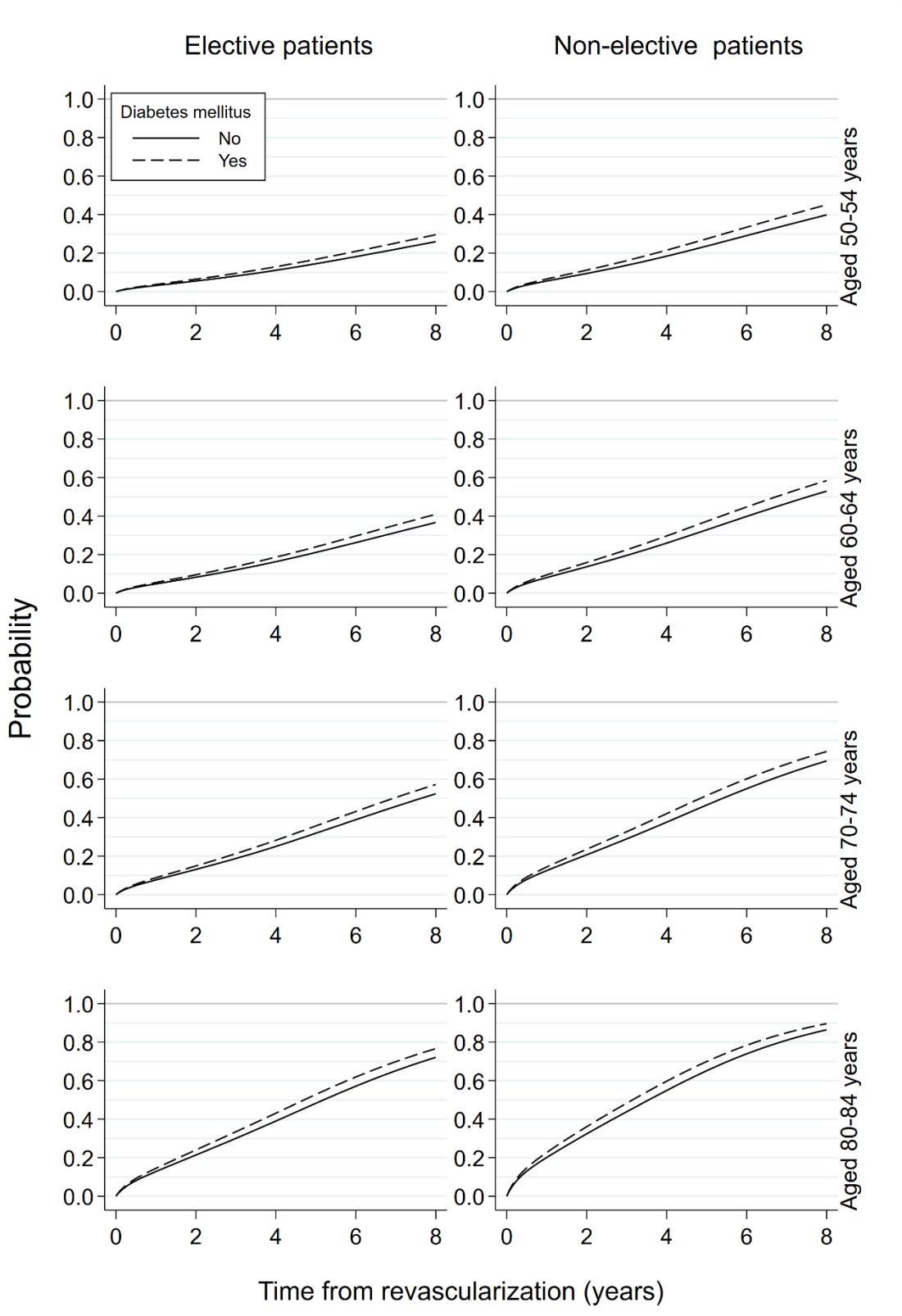


Figure S4 (b). Overall mortality after the index revascularization for elective and non-elective patients, comparison shown between the indications of tissue loss. Values of the remaining covariates were specified in Figure 3.

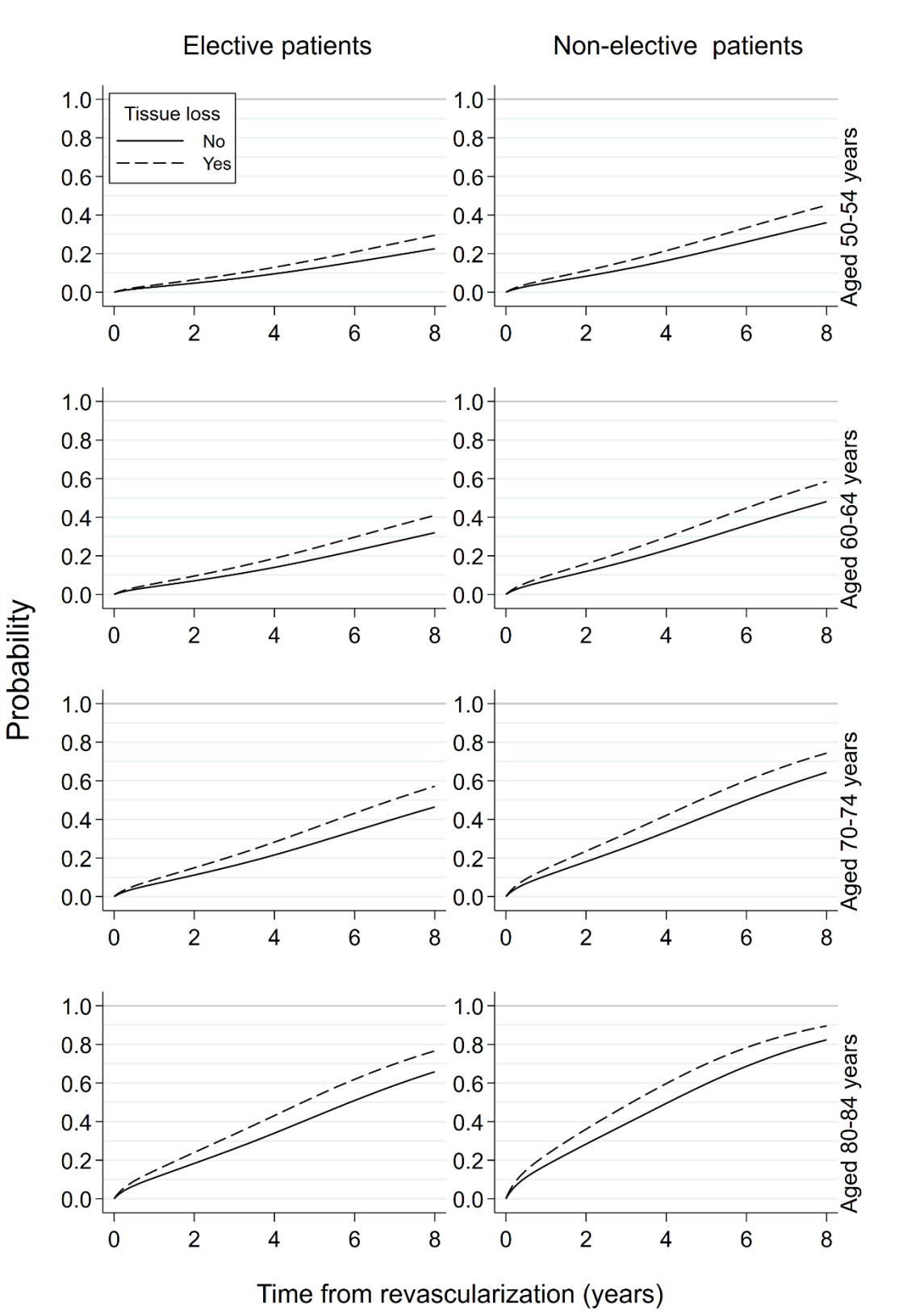


Figure S4 (c). Overall mortality after the index revascularization for elective and non-elective patients, comparison shown between patient frailty statuses. Values of the remaining covariates were specified in Figure 3.

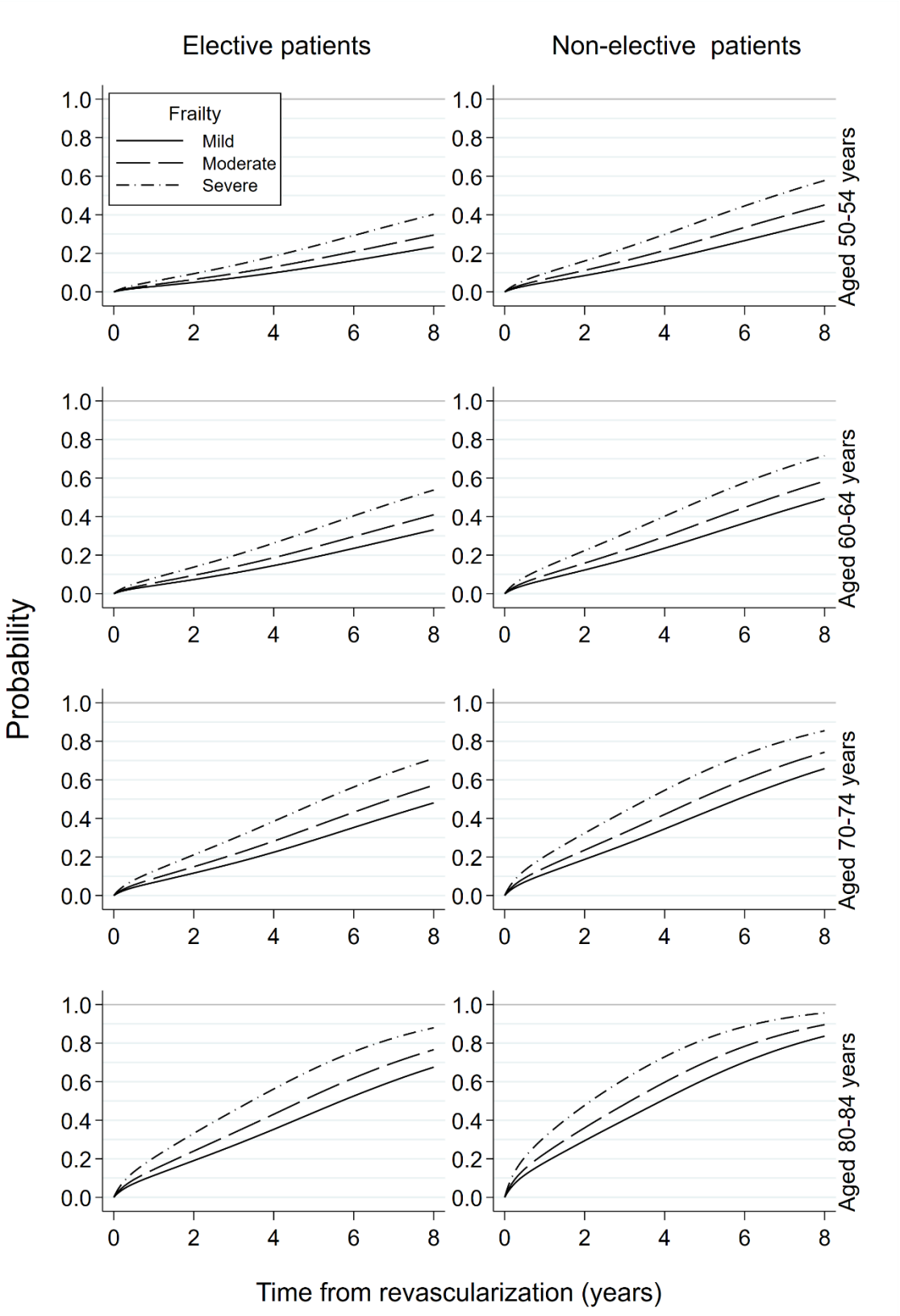


Figure S4 (d). Overall mortality after the index revascularization for elective and non-elective patients, comparison shown between RCS Charlson scores. Values of the remaining covariates were specified in Figure 3.

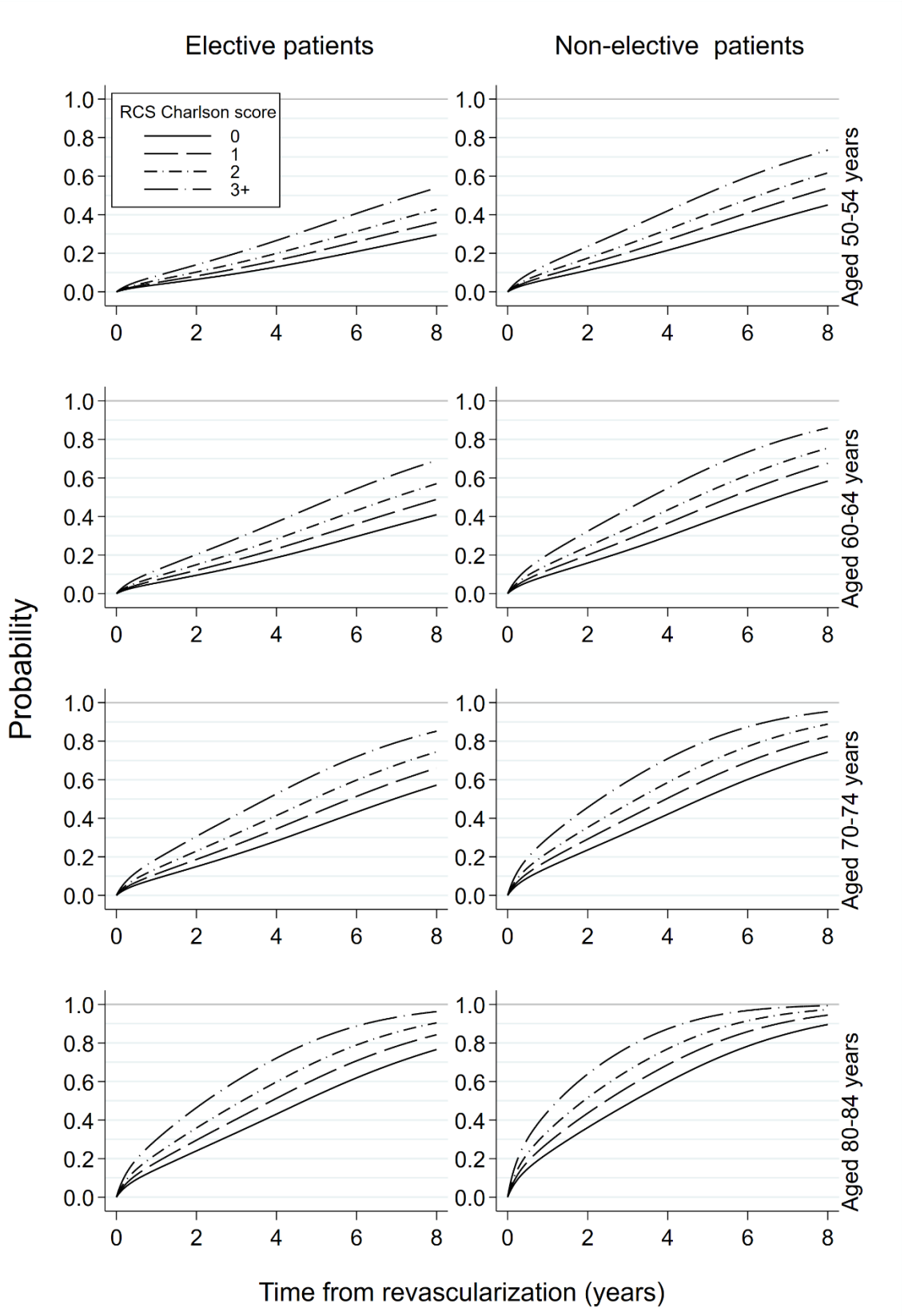
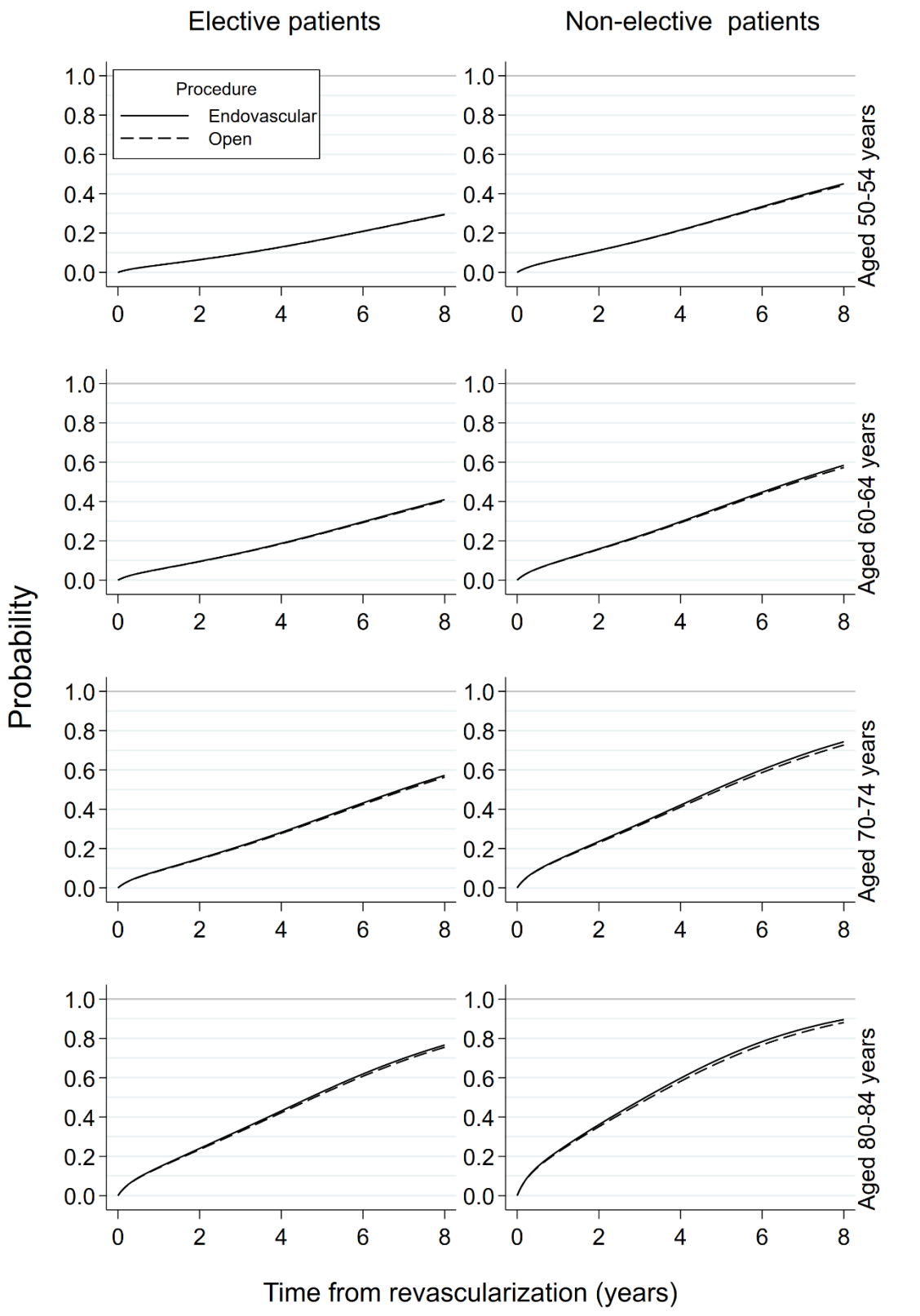


Figure S4 (e). Overall mortality after the index revascularization for elective and non-elective patients, comparison shown between the admission modes for the index revascularization. Values of the remaining covariates were specified in Figure 3.



Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a; not a match study
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment	6-8

		(measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	7
Study size	#10	Explain how the study size was arrived at	6-7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	8
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	9
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	9
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10
Participants	#13b	Give reasons for non-participation at each stage	10
Participants	#13c	Consider use of a flow diagram	n/a; participants inclusion process is simple
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	10
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	10
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	10
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	10
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their	10-11

		precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	10
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-13
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	14-16
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	17
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	17-18
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

Notes:

- 6b: n/a; not a match study
- 13c: n/a; participants inclusion process is simple The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 23. January 2024 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai