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Delays to Revascularisation and Outcomes of Non-Elective Admissions for Chronic Limb Threatening Ischaemia: a UK Population Based Cohort Study

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WHAT THIS PAPER ADDS

In this population based cohort study of 10 183 patients admitted non-electively with chronic limb threatening ischaemia undergoing infrainguinal revascularisation in England between 2017 and 2019, the one year mortality rate was 27.3% and the one year ipsilateral major amputation rate was 15.7%. Longer time from admission to revascularisation was independently associated with a higher mortality but not major amputation rate in patients with tissue loss. There was no evidence of an association between timing of revascularisation and one year outcomes in patients without tissue loss.

Objective: Major amputation and death are significant outcomes after lower limb revascularisation for chronic limb threatening ischaemia (CLTI), but there is limited evidence on their association with the timing of revascularisation. The aim of this study was to examine the relationship between time from non-elective admission to revascularisation and one year outcomes for patients with CLTI.

Methods: This was an observational, population based cohort study of patients aged $\geq$50 years with CLTI admitted non-electively for infrainguinal revascularisation procedures in English National Health Service hospitals from January 2017 to December 2019 recorded in the Hospital Episode Statistics database. Outcomes were death and ipsilateral major amputation rate at one year. Logistic regression models were fitted to explore the relationship between time to revascularisation and death, adjusted for patient and admission factors. For major amputation, multinomial logistic regression models were used to account for the competing risk of death.

Results: A total of 10 183 patients (median age 75 years) were included in the analysis, of which 67.1% (n = 6 831) were male and 57.6% had diabetes. In patients with tissue loss, the unadjusted one year mortality rate was 30.0% (95% confidence interval [CI] 28.9 — 31.0%), and for every one day increase in time from admission to revascularisation, the adjusted odds of one year death increased by 3% (odds ratio 1.03, 95% CI 1.02 — 1.04). In the absence of tissue loss, the unadjusted one year mortality rate was 19.9% (95% CI 18.4 — 21.4%) and there was no evidence of an association with time to revascularisation. There was also no statistically significant association between the time to revascularisation and risk of ipsilateral major amputation at one year irrespective of tissue loss.

Conclusion: Patients undergoing infrainguinal revascularisation during non-elective admissions for CLTI have high one year major amputation and mortality rates. Longer time from admission to revascularisation was independently associated with a higher mortality rate in patients with tissue loss, but not in those without.

Keywords: Amputation, Chronic limb threatening ischaemia, Peripheral arterial disease, Revascularisation, Time to treatment, Treatment delay
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INTRODUCTION

Chronic limb threatening ischaemia (CLTI) is a severe form of peripheral arterial disease (PAD) characterised by rest pain, ulcers, or gangrene due to reduced blood flow in the legs. It is associated with a high risk of limb loss if blood flow is not promptly restored by open surgical or endovascular revascularisation. In the UK, patients with CLTI usually present to primary care, podiatry services, or the emergency department.[1] On referral to vascular specialists, they are assessed in dedicated urgent clinics, emergency assessment wards, or the emergency department, and the decision is made to urgently admit to hospital or treat as an outpatient.[1] Delays to revascularisation can occur at various stages of the patient pathway from symptom onset to intervention.[2,3] There is currently no evidence based optimal timeframe for revascularisation of patients with CLTI recommended by national or international guidelines.[4–6]

In the UK, the Vascular Society of Great Britain and Ireland (VSGBI) published a PAD best practice framework in 2019, according to which revascularisation should be performed within five days from referral for patients urgently admitted to hospital with severe disease.[7] This recommendation was based on clinical consensus and expert opinion because there is limited evidence on the relationship between the timing of revascularisation and post-operative outcomes, even though the rates of major amputation and death after revascularisation and other factors that affect them have been extensively explored.[8–13]

Shorter time to revascularisation was associated with an increased probability of healing for ischaemic diabetic foot ulcers (hazard ratio [HR] 1.96, 95% confidence interval [CI] 1.52 – 2.52) when the time from presentation to intervention was less than eight weeks.[14] Additionally, the odds of limb salvage was three times higher in patients with CLTI and diabetes when they were revascularised within two weeks of referral (odds ratio [OR] 3.1, 95% CI 1.4 – 6.9).[15] It is hypothesised that expedited revascularisation would also decrease the risk of limb loss and death in patients without diabetes. The aim of this study was to evaluate the relationship between the timing of infrainguinal revascularisation and major amputation and mortality rates at one year for patients admitted to hospital as emergencies with CLTI.

METHODS

Study population

This population based cohort study used data extracted from the Hospital Episode Statistics (HES) Admitted Patient Care (APC) database, the national administrative hospital database that captures information about all National Health Service (NHS) hospital admissions in England.[16] The study involved secondary analysis of existing pseudo-anonymised data and was therefore exempt from NHS Ethics Committee approval. The study cohort included all patients with a PAD related diagnosis who underwent infrainguinal lower limb revascularisation procedures during non-elective admissions to NHS hospitals in England between 1 January 2017 and 31 December 2019 (Supplementary Tables S1 – S3). Combined supra- and infrainguinal revascularisation procedures were excluded. The first admission of an individual patient with a revascularisation procedure during the study period was considered the index admission, and the first revascularisation procedure was defined as the index procedure. Exclusion criteria were patients aged <50 years on the index admission, those who underwent major amputation on the same day as the index revascularisation, patients who had undergone revascularisation or major amputation in the three years prior to the index admission, and patients with an admission to revascularisation time longer than 30 days, as it was assumed that they were unsuitable for intervention in the short term (Supplementary Fig. S1). Procedures performed in NHS hospitals with fewer than an average of ten procedures per year as well as records with missing data on the covariables of interest were also excluded, and complete case analysis was performed.

Patient characteristics

Diagnostic information was recorded in HES using the International Classification of Diseases, 10th revision (ICD-10) codes.[17] The presence of diabetes mellitus and PAD was determined by the relevant ICD-10 code in any diagnostic field of the index admission and admissions in the three years prior to that, while tissue loss was indicated by ICD-10 codes for gangrene, ulcer, and osteomyelitis on the index admission (Supplementary Table S1). Comorbidity burden was calculated using the Royal College of Surgeons Charlson comorbidity index based on ICD-10 codes in the index admission and admissions in the preceding three years, excluding PAD and diabetes mellitus.[18] Frailty status (not frail, and mild, moderate, or severe frailty) was derived from diagnostic codes of the index admission and admissions in the three years prior to that using the secondary care administrative records frailty (SCARF) index.[19] As only 1.1% of patients ($n = 112$) were identified as not frail, these were grouped with patients with mild frailty for the analysis. Socioeconomic status was divided into quintiles using the Index of Multiple Deprivation 2019 of the Office for National Statistics (ONS).[20]

Office of Population Censuses and Surveys (OPCS) classification codes[21] were used to identify the revascularisation procedure side, type (endovascular or open surgical, including hybrid procedures with both open and endovascular codes), and level (femoral, popliteal, or crural, based on the bypass outflow artery or the most distal vessel treated with angioplasty or stent) (Supplementary Table S2).

Outcomes

The primary outcome was death at one year, and the secondary outcome was ipsilateral major amputation at one year after the index revascularisation procedure. Death and major amputation were also examined as time to event

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variables in the secondary outcomes (time to major amputation and time to death, respectively). Mortality data were available from the ONS death registry.[22] Major amputation was defined as any amputation proximal to the ankle joint and was available from the HES APC database.[16] The side of amputation was taken into account to capture only ipsilateral major amputations. The follow up period was calculated from the index revascularisation date to the date of death or the end of follow up (31 December 2020), whichever happened first. All patients had at least one year of follow up.

Statistical analysis

Categorical variables for patient demographics were summarised as frequencies and proportions, and differences between patient groups were examined using the χ^2 test. The median and interquartile range (IQR) were used to summarise the distributions of time to various outcomes. The difference in median between groups was examined using quantile regression.[23]

The time from admission to revascularisation had a different relationship with one year mortality depending on the presence of tissue loss; therefore, separate logistic regression models were fitted for patients with and without tissue loss. Time from admission to revascularisation was included in the models as a continuous variable. The models included the following additional variables: age group; sex; presence of diabetes; comorbidity burden; frailty status; presence of gangrene (tissue loss group only); type of procedure; and level of revascularisation. For similar reasons, the association between one year major amputation and time to revascularisation was evaluated using two separate multinomial logistic regression models, which accounted for the competing risk of death without major amputation and used those alive without major amputation as the reference category. The models contained the previous explanatory variables and social deprivation. All models satisfied the assumptions for logistic regression when tested. The Kaplan—Meier estimator was used to investigate the timing of occurrence of major amputation and death in the year after revascularisation using the cumulative incidence function, and different time to intervention groups were compared using the log rank test.

A sensitivity analysis was performed including only patients who had revascularisation procedures from 1 January 2017 to 31 December 2018, so that the one year follow up period was complete before January 2020 and excluded the coronavirus 2019 (COVID-19) pandemic period. A further sensitivity analysis that included the vascular centre procedure volume (low, medium, or high) and day of index procedure (weekday *vs.* weekend) was performed. All statistical tests were two sided, and a p value $< .050$ was considered statistically significant. All analyses were performed using STATA 17.0 (StataCorp, College Station, TX, USA). Results are presented in accordance with the Strengthening the Reporting of Observational Studies (STROBE) statement.[24]

RESULTS

Data were available for 13 497 patients who underwent infrainguinal revascularisation for PAD during non-elective admissions between 1 January 2017 and 31 December 2019. After the exclusion criteria were applied, 10 183 patients were included in the analysis (Supplementary Fig. S1), of whom 67.1% ($n = 6\,831$) were male and the median age was 75 (IQR 66, 82) years (Table 1). More than half the patients had diabetes mellitus ($n = 5\,863$; 57.6%) and 73.2% ($n = 7\,458$) had tissue loss. Overall, 54.5% of patients ($n = 5\,546$) were revascularised within five days, and the median admission to revascularisation time was five (IQR 2, 9) days. There was a greater proportion of younger patients, those without a diagnosis of diabetes or other comorbidities, less frail, and less deprived patients among those who had their procedure within five days compared with those waiting longer than five days (Supplementary Table S4). Patients with tissue loss waited longer for revascularisation (median six days; IQR 3, 10) compared with patients without tissue loss (median two days; IQR 1, 5) (Fig. 1).

Delay and mortality risk

The overall one year mortality rate after lower limb revascularisation was 27.3% ($n = 2\,776$). The relationship between time to revascularisation and adjusted mortality in patients with and without tissue loss is shown in Figure 2. For patients with tissue loss, the unadjusted mortality rate was 30.0% (95% CI 28.9 — 31.0%), and for every one day increase in time to revascularisation, the odds of one year death increased by 3% (adjusted odds ratio [aOR] 1.03, 95% CI 1.02 — 1.04; $p < .001$) (Supplementary Table S5). In the absence of tissue loss, the unadjusted one year mortality rate was 19.9% (95% CI 18.4 — 21.4%) and was not associated with the timing of revascularisation in fully adjusted models (aOR 1.00, 95% CI 0.98 — 1.03; $p = .71$). Gangrene was an independent risk factor for one year death (aOR 1.37, 95% CI 1.22 — 1.54). Other factors that were statistically significantly associated with one year death were older age, higher number of comorbidities, severe frailty, and more proximal interventions, irrespective of tissue loss status (Fig. 3).

The population attributable risk suggests that if everyone with tissue loss had a delay of no more than five days from admission to revascularisation, the mortality rate after one year would be 27.7% (95% CI 26.5 — 28.8%), which is 2.3% lower (95% CI 1.63 — 2.95%) than the current mortality rate of 30.0% (95% CI 28.9 — 31.0%), based on the current distribution of delays. No change in mortality rate would be expected in patients without tissue loss if the time to revascularisation was five days or less.

Delay and risk of amputation

At one year after revascularisation, 6 215 patients (61.0%) were alive and amputation free, 1 599 (15.7%) had undergone an ipsilateral major amputation, and 2 369 (23.3%) had died without an amputation. The median time to revascularisation was four (IQR 2, 8) days for those who were alive and amputation free at one year, five (IQR 2, 8)

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Table 1. Baseline characteristics of patients (n = 10183) stratified by the presence of tissue loss.

Characteristic	Total (n = 10183)	Tissue loss (n = 7458)	No tissue loss (n = 2725)	p value*
Age group − y				<.001
50–59	1207 (11.9)	818 (11.0)	389 (14.3)	
60–69	2241 (22.0)	1578 (21.1)	663 (24.3)	
70–79	3218 (31.6)	2349 (31.5)	869 (31.9)	
≥80	3517 (34.5)	2713 (36.4)	804 (29.5)	
Sex				<.001
Male	6831 (67.1)	5120 (68.7)	1711 (62.8)	
Female	3352 (32.9)	2338 (31.3)	1014 (37.2)	
Diabetes mellitus	5863 (57.6)	4907 (65.8)	956 (35.1)	<.001
Charlson comorbidity index				<.001
0	2858 (28.1)	1962 (26.3)	896 (32.9)	
1	2775 (27.2)	1973 (26.5)	802 (29.4)	
2	2042 (20.1)	1537 (20.6)	505 (18.5)	
≥3	2508 (24.6)	1986 (26.6)	522 (19.2)	
SCARF frailty index				<.001
Mild	888 (8.7)	343 (4.6)	545 (20.0)	
Moderate	2599 (25.5)	1668 (22.4)	931 (34.2)	
Severe	6696 (65.8)	5447 (73.0)	1249 (45.8)	
Deprivation†				.098
Q1	1522 (14.9)	1104 (14.8)	418 (15.3)	
Q2	1790 (17.6)	1331 (17.9)	459 (16.9)	
Q3	2032 (20.0)	1450 (19.4)	582 (21.4)	
Q4	2227 (21.9)	1624 (21.8)	603 (22.1)	
Q5	2612 (25.6)	1949 (26.1)	663 (24.3)	
Procedure type				<.001
Endovascular	6946 (68.2)	5631 (75.5)	1315 (48.3)	
Open	3237 (31.8)	1827 (24.5)	1410 (51.7)	
Level of intervention				<.001
Femoral	4944 (48.6)	3420 (45.9)	1524 (55.9)	
Popliteal	2264 (22.2)	1570 (21.0)	694 (25.5)	
Crural	2975 (29.2)	2468 (33.1)	507 (18.6)	

Data are presented as n (%). SCARF = secondary care administrative records frailty.
* p values were derived using the χ^2 test for the difference between the two groups.
† Q1 = least deprived; Q5 = most deprived.

days for patients with a major amputation, and six (IQR 3, 11) days for those who died without major amputation (p < .001). The estimated one year amputation rate was 16.4% (95% CI 15.5 — 17.2%) for patients with tissue loss and 13.9% (95% CI 12.6 — 15.1%) for patients without tissue loss.

The relationship between time from admission to revascularisation and estimated one year major amputation rate is shown in Figure 4. There was no significant association between time to revascularisation and risk of

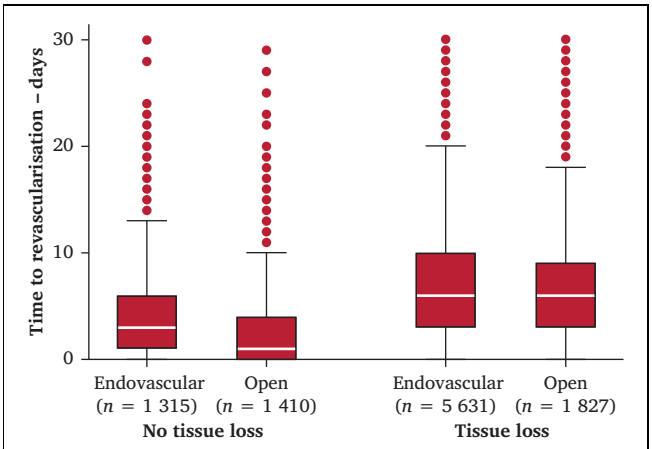

Figure 1. Boxplots illustrating the distribution of time from admission to revascularisation in patients with chronic limb threatening ischaemia, stratified by the presence of tissue loss and procedure type.

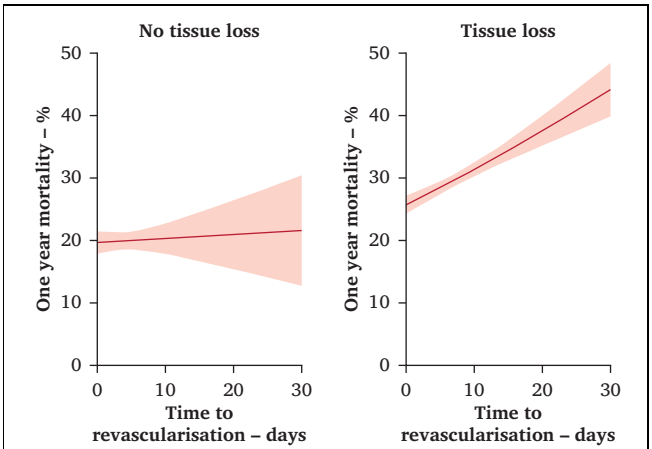

Figure 2. Marginal estimate of the association between adjusted one year mortality and time from admission to revascularisation in patients with chronic limb threatening ischaemia, stratified by the presence of tissue loss.

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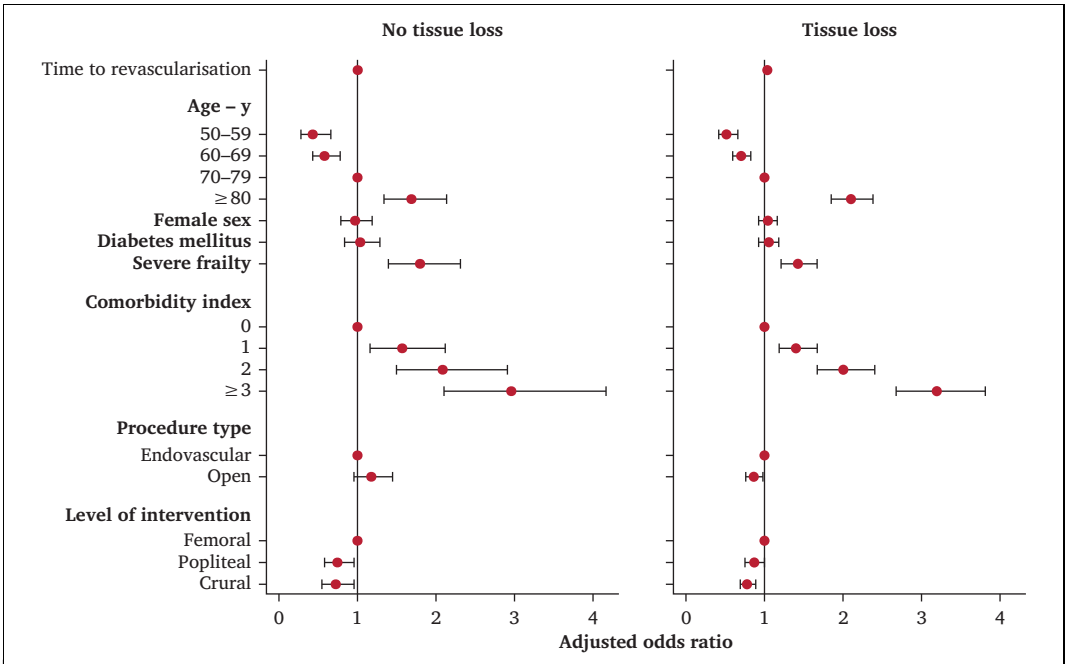

Figure 3. Coefficients plot indicating the adjusted odds ratio and 95% confidence interval for mortality at one year from separate multivariable logistic regression models in patients with and without tissue loss.

ipsilateral major amputation at one year in the tissue loss (aOR 0.999, 95% CI 0.99 — 1.01) and no tissue loss (aOR 1.02, 95% CI 0.99 — 1.05) groups after controlling for patient and admission factors and taking into account the competing risk of death (Fig. 5).

Different factors were associated with increased risk of one year major amputation depending on whether the patient had tissue loss or not, apart from severe deprivation, which was a statistically significant factor in both groups (aOR 1.36, 95% CI 1.06 — 1.75 in no tissue loss group; aOR 1.22, 95% CI 1.06 — 1.41 in tissue loss group) (Supplementary Table S6). In patients without tissue loss, crural vessel intervention was also independently associated with an increased risk of one year major amputation (aOR 2.74, 95% CI 2.09 — 3.59 *vs.* femoral). In patients with tissue loss, statistically significant factors included multiple comorbidities (aOR 1.42, 95% CI 1.15 — 1.75 for three or more comorbidities *vs.* none), severe frailty (aOR 1.25, 95% CI 1.05 — 1.49 *vs.* mild frailty), and presence of gangrene (aOR 2.02, 95% CI 1.73 — 2.35). On the other hand, females and people aged ≥80 years were less likely to have a major amputation at one year in the tissue loss group (aOR 0.83, 95% CI 0.72 — 0.96 for female *vs.* male; aOR 0.75, 95% CI 0.63 — 0.89 for ≥80 years *vs.* 70 — 79 years age group) (Fig. 5).

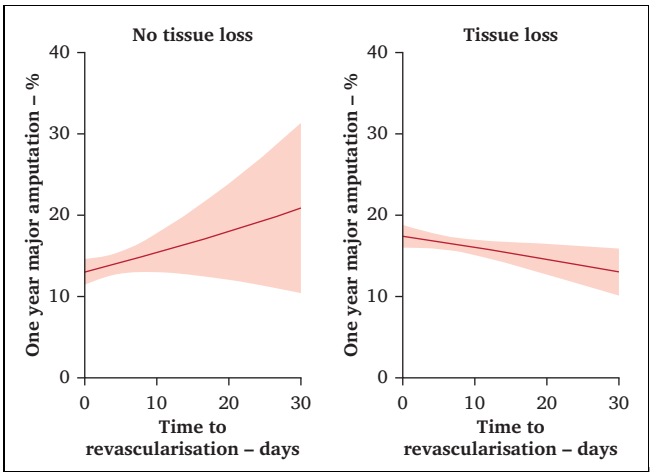

Figure 4. Marginal estimate of the association between adjusted one year ipsilateral major amputation and time from admission to revascularisation in patients with chronic limb threatening ischaemia, stratified by the presence of tissue loss.

Delay and time to first event (major amputation or death)

Whereas mortality increased at a steady rate over time (Fig. 6), the incidence of ipsilateral major amputation sharply increased in the first two months after revascularisation and continued to increase at a lower rate from six months onwards. For patients who had an amputation in the first year after revascularisation, the median time to major amputation was 35 (IQR 10, 98) days, with the 30 day major amputation rate being 7.4% ($n = 752$). A longer interval between admission and revascularisation was associated with a higher mortality rate, with the difference becoming more prominent over time, especially in the tissue loss group (Fig. 6).

A sensitivity analysis of 6 843 patients treated in 2017 and 2018 yielded similar results regarding the association between revascularisation delay and outcomes. The one year overall mortality rate was 27.9% ($n = 1\,910$), indicating that the overall mortality was unlikely to have been influenced by the COVID-19 pandemic. There was no change in

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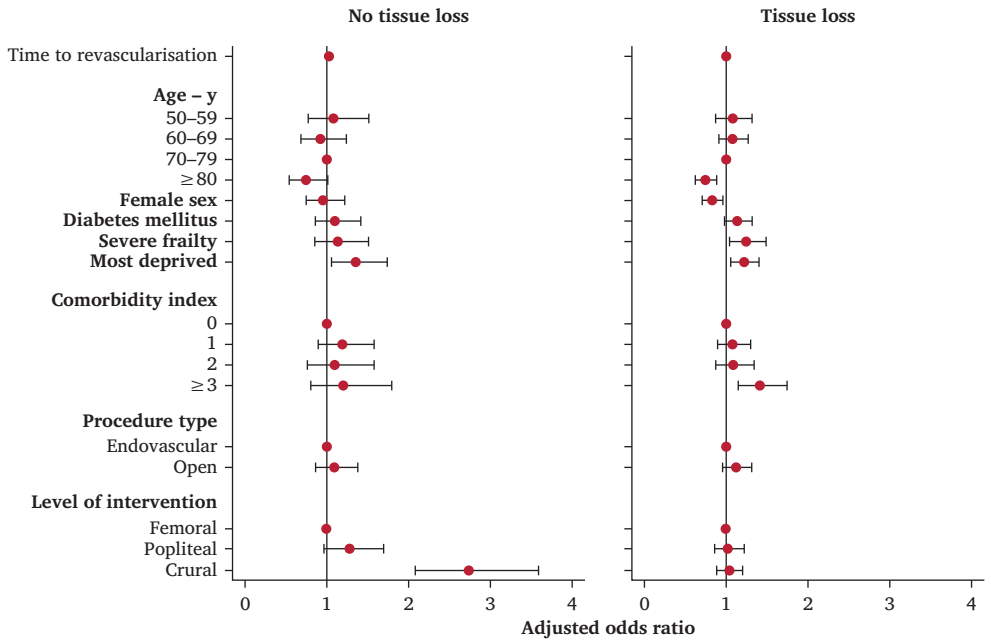

Figure 5. Adjusted odds ratio and 95% confidence interval for ipsilateral major amputation at one year for various patient and admission factors by the presence of tissue loss.

the association between time to revascularisation and the outcomes after further adjustment for vascular centre procedure volume and day of procedure (Supplementary Table S7).

DISCUSSION

In this study of 10 183 patients with CLTI undergoing infrainguinal revascularisation during non-elective admissions in England between 2017 and 2019, the overall one year mortality rate was 27.3% and the one year ipsilateral major amputation rate was 15.7%, with most amputations occurring in the first few months after revascularisation. The mortality rate was similar to the reported 28% in a German cohort study of 199 953 patients hospitalised with CLTI,[25] but higher than rates of 12 — 24% in meta-analyses of CLTI revascularisation studies[10,26] and rates of 11 — 13% in English cohort studies.[27,28] The difference in mortality rates may be due to the fact that the current study cohort was limited to non-elective admissions, with a high proportion of tissue loss and a third of the patients being aged ≥80 years, all of which are associated with higher mortality. The randomised controlled trials reported in the meta-analyses often excluded high risk and very elderly patients who are included in real world studies such the current study and have a higher mortality risk. The one year major amputation rate after revascularisation in patients with CLTI ranged 8 — 24%, similar to the reported rate of 15.7% in the current study.[10,29,30]

The median admission to revascularisation time was five (IQR 2, 8) days; therefore, only half of patients were treated in the timeframe recommended by the VSGBI guidelines.[7] This is unsurprising, as the guidance was published in April 2019 and most of the procedures in this study were performed prior to that date. Time to revascularisation was longer for patients with tissue loss compared with those without, indicating that patients with a more severe presentation waited longer for revascularisation. This finding is congruent with other studies that have identified the increased severity of PAD as a factor associated with revascularisation delays.[31,32] The reasons for delays in the presence of tissue loss may include the need for pharmacological treatment such as antibiotics, other procedures such as debridement to control foot sepsis, additional imaging, cardiovascular investigations, or medical optimisation prior to the revascularisation procedure. Other factors contributing to delays include older age, greater burden of comorbidities, the hospital procedure volume, presentation in a hub or spoke hospital, and the weekday of admission.[31,32] Delays in older and more comorbid individuals may be associated with the complex decision-making required to identify the best treatment option and weigh revascularisation against conservative management or primary amputation. In this study, it was not possible to determine whether the delay was for logistical reasons, such as surgical or interventional suite capacity, or to patient need for optimisation and additional investigations, the latter indicating a more severe clinical condition.

The association between death and delay to operative management has been demonstrated in patients with hip fractures[33] and those undergoing major amputation,[34] but to the authors' knowledge it has not been explored in patients undergoing inpatient revascularisation following non-elective admission for CLTI.[2] In the current study, it was found that a longer interval from non-elective admission to revascularisation in patients with tissue loss was

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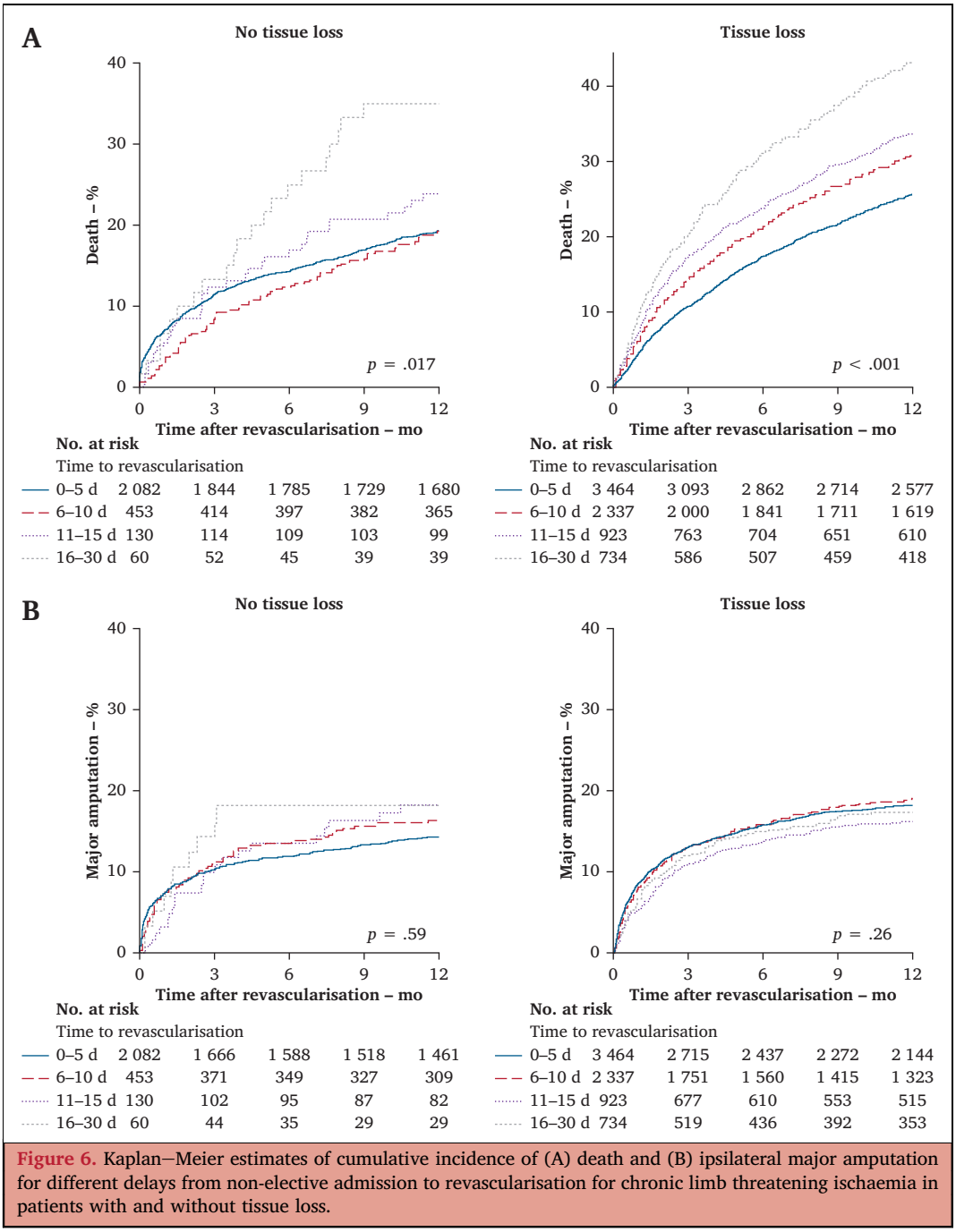

Figure 6. Kaplan–Meier estimates of cumulative incidence of (A) death and (B) ipsilateral major amputation for different delays from non-elective admission to revascularisation for chronic limb threatening ischaemia in patients with and without tissue loss.

independently and statistically significantly associated with increased one year mortality. The more prominent negative effect of delays in patients with tissue loss may have been related to their physiological state, which was probably worse compared with patients with less severe presentations, so they may have decompensated while waiting for a procedure in the hospital. Even though the results were adjusted for patient comorbidities and frailty, physiological measurements such as blood pressure and heart rate or biochemical markers that have influenced these outcomes in other studies were not available.[35]

Patients with tissue loss had a higher mortality rate in this study compared with patients revascularised in the absence of tissue loss. These findings are supported by a large cohort study of 38 470 patients from the US Vascular Quality Initiative, which reported a 50% higher two year mortality rate in the tissue loss group (HR 1.5, 95% CI 1.2 — 1.9).[8] Similarly, Vierthaler *et al.* found that patients with rest pain had a 13% mortality rate at one year compared with 20% in patients with tissue loss.[36] Other factors associated with a higher one year mortality rate in the current study included the comorbidity burden, age, and frailty, which with the possible exception of frailty, are non-modifiable.

It was hypothesised that a longer interval from admission to revascularisation would be associated with a higher risk of major amputation. A delay of more than two weeks from

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referral to revascularisation has been associated with three fold increased risk of major amputation in patients with diabetes and CLTI, but not in patients without diabetes.[15] A further study of patients with ischaemic diabetic foot ulcers demonstrated that shorter time from presentation to revascularisation ($\leq$8 weeks) was associated with an increased probability of healing (HR 1.96, 95% CI 1.52 — 2.52).[14] There was, however, no association between time to revascularisation and one year major amputation in the current study, possibly because delays from the onset of symptoms prior to presentation were not taken into account and may have considerably varied.[2] However, patients with disease so severe that they required inpatient intervention would be expected to seek healthcare advice soon after symptom onset.

Strengths and limitations

This study has several strengths. It included a large population cohort covering all admissions to NHS hospitals in England, and follow up information was available for all patients for at least a year. Additionally, the risk of amputation was reported separately from the risk of death, instead of the composite outcome of amputation free survival, and the competing risk of death was taken into account when reporting the estimated risk of ipsilateral major amputation. Finally, the results are unlikely to have been influenced by the COVID-19 pandemic, as a sensitivity analysis excluding that time period generated similar results.

This study also has various limitations. First, the data source was an administrative database that does not optimally collect the severity of PAD;[37] therefore, some patients with CLTI may have been excluded. The HES database is also prone to errors, such as omission of clinical information or inaccurate coding, but overall the coding has been deemed sufficiently robust for use in research.[38,39] Additionally, the results were adjusted for many patient and admission characteristics, but there may have been residual confounding factors, such as smoking, atherosclerotic burden, and biochemical markers.[35] The observational study design also limited extending the observed associations to inferences about causal effects, and it was not possible to determine whether the delay was due to clinical reasons or capacity issues. It should also be noted that calculation of the population attributable risk makes an implicit assumption about a causal relationship between time to revascularisation and the outcomes, and its overinterpretation is cautioned against. It was derived to translate the ORs into a measure that illustrates the potential benefit of reducing time to revascularisation that might be possible. Finally, the study only included patients without prior revascularisations or major amputations; therefore, the results are applicable to this patient cohort.

Conclusion

Patients undergoing infrainguinal revascularisation during non-elective admissions for CLTI have high one year major amputation and mortality rates of 16% and 27%, respectively. A longer interval between admission and revascularisation was independently associated with a higher mortality rate in patients with tissue loss in this study, but there was no evidence of association with major amputation. Given the very limited evidence in this area in the literature, more studies are required to support or refute the current findings and to provide the basis for national recommendations, and time to revascularisation should be routinely reported in studies exploring revascularisation outcomes.

CONFLICTS OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2024.12.038.

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