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Five year mortality and hospital costs associated with surviving intensive care

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At a glance commentary

Scientific Knowledge on the Subject

There are increasing number of patients surviving an episode of critical illness. Recent cohort studies indicate that intensive care survivors may have ongoing complex and potentially costly health care needs. However, robust population-level estimates of the excess mortality and health care costs associated with surviving intensive care are needed.

What this study adds to the field

We have demonstrated an increased risk of death (33%) and hospital readmission rate (22%) in patients surviving an episode of intensive care compared with hospital controls in the five years after discharge from hospital after adjusting for important confounders. Our population-level estimates indicate substantial costs associated with ICU survivorship which can be used to inform health policy.

Role of the funding source

The project was funded through a fellowship from the Chief Scientist Office for Scotland. The funder had no role in any of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Authors' contributions

NL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. NL, TW, SW, KM and GM contributed to conception and design of the work. NL, MG, CH and RD contributed to data acquisition and analysis. All authors contributed to interpretation of data for the work. NL and TW drafted the work. All authors revised it critically for important intellectual content. All authors gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Provisional data analyses were presented in abstract form at scientific meetings (UK Intensive Care Society Annual State of the Art Meeting 2013 and 2014).

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Abstract

Rationale

Survivors of critical illness experience significant morbidity, but the impact of surviving ICU has not been quantified comprehensively at a population level.

Objectives

To identify factors associated with increased hospital resource use and to ascertain if ICU admission was associated with increased mortality and resource use.

Methods

Matched cohort study and pre-post analysis using national linked data registries with complete population coverage. Population: patients admitted to all adult general ICUs during 2005 surviving to hospital discharge identified from the Scottish Intensive Care Society Audit Group (SICSAG) registry; matched (1:1) to similar hospital controls. Five-year outcomes: mortality, hospital resource use. Confounder adjustment: multivariable regression and pre-post within-individual analyses.

Measurements and Main results

5259 from 7657 ICU patients survived to hospital discharge (5215 (99.2%) matched to hospital controls). Factors present pre-ICU admission (comorbidities/pre-ICU hospitalisations) were stronger predictors of hospital resource use than acute illness factors. In the five years after the initial hospital discharge compared with hospital controls, the ICU cohort had higher mortality (32.3% versus 22.7%, hazard ratio 1.33,95%CI 1.22 to 1.46,p<0.001), used more hospital resources (mean hospital admission rate 4.8 versus 3.3/person/5years) and had 51% higher mean five-year hospital costs ($25608 versus $16913/patient). Increased resource use persisted after confounder adjustment (p<0.001) and using pre-post analyses (p<0.001). Excess resource use and mortality was greatest for younger patients without significant comorbidity.

Conclusions

This complete, national study demonstrates that ICU survivorship is associated with higher five-year mortality and hospital resource utilisation than hospital controls representing a substantial burden on individuals, care-givers and society.

Keywords

Intensive care; mortality; hospital readmission; hospital costs; registries

Introduction

Survivors of critical illness suffer significant morbidity,(1) including neuromuscular complications,(2) respiratory impairment,(3) cognitive decline,(4) psychological morbidity,(5) and physical disability.(3) Patients report low quality of life, especially in physical domains.(6, 7)

The decline in physical, psychological, and/or cognitive function following critical illness has been termed the 'post-intensive care syndrome'.(8) The prevalence and severity of different morbidities have been described in cohort studies, but these provide limited information about the healthcare burden of the post-intensive care syndrome due to selection bias, loss to follow-up, and limited healthcare resource utilisation data.(9) Furthermore, the magnitude of the healthcare burden and duration over which it remains elevated is poorly understood.(10) Linkage of national healthcare registries provides a more complete, national picture of longer-term outcomes for intensive care unit (ICU) survivors. Comparing ICU survivors to matched hospital or general population cohorts also provides a method of exploring the magnitude of excess mortality and healthcare resources associated with ICU survivorship and identifying patients at greatest risk.

We hypothesised that indirect evidence of the clinical and financial burden of post-intensive care syndrome could be demonstrated through identifying higher longer-term mortality and hospital resource utilisation in ICU survivors compared with control populations in the years following ICU admission. We aimed to: 1) compare longer-term mortality for a national, cohort of ICU survivors over a five year period following hospital discharge cohort with hospital controls (hospitalised patients not receiving intensive care) and general population mortality rates; 2) identify factors associated with increased post-discharge hospital resource use; 3) compare longer-term hospital resource use for the ICU cohort with hospital controls; and 4) compare hospital resource use in the years following an ICU admission with baseline hospital resource use within individuals. Some provisional results of these studies have been previously reported in the form of abstracts.(11-13)

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Methods

Study population, setting and databases

We used cohort study designs (matched and pre-post within-individual analyses). Primary data sources were routinely collected, administrative, linked registries derived from the Scottish Intensive Care Society Audit Group (SICSAG), Scottish Morbidity Record of acute hospital admissions (SMR01) and Scottish death records. The SICSAG registry captures all adult general intensive care activity within Scotland. In 2005 all 24 adult general ICUs, serving a population of 5.1 million (4.2 million aged ≥16), submitted data.(14) The ICU cohort comprised residents aged ≥16 admitted to general ICUs in Scotland between 1st January and 31st December 2005 who survived to hospital discharge (index admission). All ICU patients were eligible regardless of length of ICU stay. For multiple admissions, only first ICU admissions with a valid linkage number were included. The matched hospital cohort was extracted from the SMR01 registry using identical inclusion and exclusion criteria, but excluded hospital admissions with ICU episodes. Matching was undertaken 1:1 using age (in ten-year age bands), sex, admission type (emergency surgical, elective surgical, emergency medical) and date of hospital discharge (quarter of year). Approvals were obtained from the relevant data-governing bodies (Privacy Advisory Committee, NHS Scotland Information Services Division; ref 55/09). All data were anonymised prior to release to the researchers. The South East Scotland Research Ethics Committee granted a waiver (ref NR/1001AB14). The eSupplement provides further details regarding the registries.

Outcomes and follow-up period

The primary outcomes were mortality and hospital resource use. Mortality for ICU and hospital cohorts was derived from linkage to Scottish death records. General population mortality rates were obtained by indirect standardisation using the general Scottish population as a reference population.(15) Age and sex specific mortality rates were derived from national Scottish mortality data and applied to the ICU cohort population structure to produce expected mortality. Hospital

resources comprised elective (scheduled) day-case, elective (scheduled) inpatient or emergency (unscheduled) inpatient acute hospital admissions and were quantified in four ways: total number of hospital admissions; total number of days spent in hospital; total costs of hospital care; and cumulative incidence of first admission (in sensitivity analyses). Costs of hospital care included only day-case and inpatient admissions. Per diem costs for hospital care were derived from the NHS Scottish Costs Book(16) and converted to 2014 costs using Purchasing Power Parities. Measures of hospital resource use were calculated per person over the five-year follow-up period (see eSupplement). Follow-up commenced from the day of index hospital discharge and ended at five years (with censoring on 31/12/2010 at study end). As censoring was negligible and emigration in older age groups from Scotland to the remainder of the UK or overseas is known to be low,(17) follow-up was assumed to be complete for analyses (missing person-time<0.2% for all cohorts).

Statistical analysis

All analyses were undertaken using Stata IC version 13 (StataCorp LP, Texas, USA). For more information see eSupplement.

Mortality (ICU cohort versus hospital control versus general population): We used Kaplan-Meier survival plots to compare the ICU cohort, hospital cohort, and expected age/sex indirectly standardised survival curves derived from the general Scottish population mortality rates. Cox regression stratified by matched pairs was used to estimate the hazard ratio (HR) for mortality in ICU versus hospital controls adjusted for potential confounders. In addition to matched variables, we adjusted for the following: age, quintile of an area-based measure of socio-economic status (social index of multiple deprivation, SIMD),(18) remoteness,(19) rurality,(19) health region, pre-index hospitalisation health care resource use (number of hospital admissions in the prior five years), and number of comorbidities from the Charlson index (reconstructed from diagnostic codes on admission records in prior one year).(20) Measures of illness severity were not included as these were not available for the hospital controls. For more information see eSupplement.

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Predictors of resource use (ICU cohort only): Independent predictors of number of hospital admissions over five years were identified for the whole ICU cohort using a negative binomial multivariable regression model (see eSupplement). This analysis was limited to individuals in the ICU cohort. Coefficients produced from this regression model - once exponentiated - can be interpreted as an admission rate ratio. This is because it represents the ratio of admission rates in one group compared with the reference group. Variables were grouped into demographic factors, prior illness/resource use factors and index admission factors. We specifically assessed the association of several acute illness factors with resource use in additional analyses due to collinearity: Simplified Acute Physiology Score II (SAPS II) on ICU admission, organ support (provision of mechanical ventilation, renal replacement therapy or cardiovascular support), total number of organs supported, ICU length of stay (LOS), post-ICU hospital LOS and total hospital LOS (see eSupplement).

Resource use (ICU cohort versus hospital controls): The first approach to explore potential excess resource use on a relative scale associated with ICU admission was a comparison of *matched ICU and hospital controls.* We estimated admission rate ratios using negative binomial regression to model the number of hospital admissions during the five year follow up period, allowing for the matched nature of the data by using standard errors that accommodated clustering (correlation between matched pairs).(21) Potential confounders were included in the multivariable model as for mortality analyses. We explored effect modification by reporting stratum-specific admission rate ratios and including interaction terms in regression models for the following variables: age (dichotomised <70, ≥70 years) and presence of any Charlson comorbidity (dichotomised 0, ≥1).

Resource use (pre-post within-individual; ICU cohort only): The second approach to explore potential excess resource use associated with ICU admission was a pre-post comparison *within individuals* on an absolute scale. This analysis was limited to individuals in the ICU cohort. We calculated excess post-discharge hospital costs by subtracting baseline hospital costs (those that would have accrued had the patient not been admitted to ICU) from post-discharge hospital costs during the time spent

alive and under follow-up. Baseline hospital costs were derived from hospital admissions during the period before index hospital admission, varying this period from 1-5 years pre-index admission for each patient (see eSupplement). No adjustment for confounders was undertaken as confounding was controlled by comparisons within individuals. However, we modelled the uncertainty of the effect of increasing age during follow-up on hospital costs and the uncertainty of baseline costs by varying these under six scenarios in additional analyses to (see eSupplement).

Sensitivity analyses

Resource use: For analyses to identify predictors of resource use and comparing resource use in the ICU cohort and hospital controls, we performed a sensitivity analysis using Fine and Gray competing risks.(22) This allows for the competing risk of death by modelling an estimate of cumulative incidence of first hospital admission with early deaths remaining in the denominator. Exponentiated regression coefficients can be interpreted as sub-hazard ratios (SubHR).(23) This sensitivity analysis was important because in both negative binomial external-controlled and pre-post within-individual analytical approaches above, people who die do not subsequently accrue costs. Patient groups with high, early mortality, therefore, would be less likely to accrue substantial healthcare resource use over the five-year follow up period. However, this sensitivity analysis using competing risks regression differs from the other two approaches as the outcome being modelled is cumulative incidence of *first* hospital admission whereas the other approaches model the total number of admissions or total hospital costs during the follow up period.

Results

Baseline characteristics

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In 2005, 5259 patients out of 7656 survived to hospital discharge after an index ICU admission (eFigure 1); 5215 (99.2%) were successfully matched to a hospital control (eTable 1). ICU patient cohort characteristics are shown in eTable 1. Median age was 60 years (IQR 44-72), 61% were mechanically ventilated, 73% had ≥1 hospital admission during the prior five years, and 27% had ≥1 pre-existing Charlson comorbidities. Median ICU LOS was 2 days (IQR 1-5, mean 5) and median hospital LOS was 17 (IQR 9-39, mean 34). Compared with matched hospital controls, the ICU cohort were more likely to live in areas of socio-economic deprivation (p=0.001), had more comorbidities (p<0.001), and had greater numbers of previous hospital admissions (p<0.001) (Table 1).

Mortality

Mortality for the ICU cohort at one year was 10.9% (95% confidence interval (CI) 10.0 to 11.7) and at five years was 32.3% (95%CI 31.0 to 33.6) (Figure 1). Mortality in the ICU cohort was higher than for matched hospital controls (one year 7.5%; five year 22.7%) and for an age-sex standardised general population (one year 2.2%; five year 13.4%). After adjustment, the relative risk of death for the ICU cohort was 33% higher, during five year follow-up period, than for hospital controls (unadjusted HR 1.56, 95%CI 1.41 to 1.67; adjusted HR 1.33, 95%CI 1.22 to 1.46, p<0.001). On stratification by age, relative mortality was substantially higher in those aged <70 years (HR 1.68, 95%CI 1.47 to 1.92, p<0.001) but was similar for survivors aged ≥70 compared to hospital controls (HR 1.05, 95%CI 0.92 to 1.19, p=0.45; interaction term, p<0.001). Comorbidity was not found to be a statistically significant effect modifier (interaction term, p=0.09).

Resource use

Over the five-year follow-up period, 81.7% of the ICU cohort had ≥1 hospital admission with a mean 4.8 hospital admissions per patient (accounting for 173,113 days in hospital, mean 32.9 hospital days per patient; accounting for 2.2% of days alive) (eTable 2). Total costs were $136.1 million, equivalent to $25881 per person/individual in the ICU cohort over the five-year follow-up period. Emergency

admissions to hospital comprised 54% of all hospital admissions, accounting for 77% of hospital days and 75% of hospital admission costs (Figure 2).

Within the ICU cohort, factors associated with the number of hospital admissions over the five-year follow-up period are presented in eTable 3a. Comparing factors grouped into three categories (demographics, prior illness/resource use, and index admission factors), the strongest predictors (based on Wald χ^2 statistic) were prior illness/resource use factors (χ^2=420.6, 4df, p<0.001), followed by index admission factors (χ^2=140.1, 34df, p<0.001), and demographic factors (χ^2=41.1, 10df, p<0.001). ICU admission diagnoses in the ICU cohort associated with hospital admission are shown in eTable 3b; oesophageal variceal bleeding was associated with the highest admission rate ratio (ARR). Competing risk of death analysis yielded similar results for most covariates (eTable 3a and 3b). Where differences existed (e.g. age), these largely reflected differences in mortality (oldest vs youngest 52% vs 12%) and therefore a shorter follow up time to experience readmissions. This led to a lower admission rate ratio produced by the negative binomial analysis which did not substantially affect competing risks analyses. Most markers of ICU acute severity of illness and index hospitalisation were either weakly or not associated with five-year hospital admission rate or cumulative incidence of first admission (eTable 4). The strongest association was with hospital LOS.

Resource use: ICU cohort versus hospital controls

During the five-year follow-up period, the mean time under follow-up whilst alive was 4.02 years/person in the ICU cohort compared with 4.30 year/person in hospital controls. Compared with controls, the ICU cohort were more likely to have ≥1 hospital admission (81.6% versus 73.3%), used more hospital resources (admission rate 4.8 versus 3.3 per person/5 years; ARR 1.47, 95%CI 1.38 to 1.57, p<0.001); had a higher number of mean days in hospital (32.6 versus 21.5; 2.2% versus 1.4% of days alive) and had a 51% higher mean costs of hospital admissions ($25608 versus $16912 per patient; $133.5million versus $88.2mililon for whole cohort) (Table 2). The majority of costs for both

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cohorts was attributable to emergency hospital admissions (ICU cohort: mean $19078; 74.5% of total costs; hospital controls: $12239; 72.4% of total costs).

After adjusting for potential confounders, the relative rate of hospital admission in the five-year period remained significantly higher for the ICU cohort (ARR 1.22, 95%CI 1.15 to 1.30, p<0.001). Allowing for competing risk of death by modelling cumulative incidence of first hospital admission, the ICU cohort had a 19% increased risk of hospital admission compared with hospital controls (SubHR 1.19, 95%CI 1.13 to 1.24, p<0.001).

To account in part for differences in mortality rates between ICU and hospital cohorts, a comparison of annual hospital resources used per patient alive at the start of each year was undertaken. This demonstrated a reduction in hospital resource use for each year of follow-up in both cohorts, but this remained higher in the ICU cohort throughout (Table 2). After adjusting for confounding, the ICU cohort had higher hospital admission rates for each year of follow-up which persisted in the fifth year of follow-up (Year 1: ARR 1.30, 95%CI 1.20 to 1.41, p<0.001; Year 5 ARR 1.19, 95%CI 1.07 to 1.32, p=0.002).

Effect modification: The adjusted excess rate of five-year hospital admissions (on a relative scale) in the ICU cohort, compared with hospital controls, varied by age and comorbidity (Figure 3). On stratification by age, relative hospital admission rates for the ICU cohort compared to hospital controls were higher for people <70 years (ARR 1.28, 95%CI 1.18 to 1.38, p<0.001) than for those aged ≥70 years (ARR 1.09, 95%CI 1.00 to 1.19, p=0.05; interaction term p<0.001) (Figure 3). In competing risks analyses, age was an effect modifier (interaction term p<0.001) but comorbidity was not (p=0.26) (eFigure 2).

Resource use: pre-post within-individual analysis

For individuals in the ICU cohort, mean five-year post-discharge hospital costs were greater than baseline cost of hospital care, derived from hospital costs in the year before ICU admission (mean difference from baseline $7919 per person (95%CI $6324 to $9516, p<0.001). Mean annual hospital costs were greater than baseline costs for each year of follow-up (Figure 4). These were highest for the first year ($9349; difference from baseline $4239, 95%CI $3670 to $4809, p<0.001), and lowest for the fifth year ($4670; difference $724, 95%CI $200 to $1248, p=0.007). Under all six scenarios of varying baseline costs and including effects of ageing, subsequent hospital costs were higher than baseline for the first year after hospital discharge; for the third year, the five scenarios still indicated higher hospital costs than baseline; for the fifth year, this had reduced to three scenarios (Figure 4).

Discussion

This national, complete cohort of ICU patients experienced significantly higher mortality and used more hospital resources in the five years after hospital discharge compared with hospital survivors who did not require ICU admission. The excess resource use persisted throughout five-year follow-up. Factors present prior to ICU admission were much stronger predictors of hospital resource use than those associated with the acute illness. The excess mortality and use of hospital resource was most pronounced in patients under 70 years of age and those with no pre-existing illness.

The persisting excess mortality and hospital costs associated with ICU survivorship is likely to result from a complex interplay between pre-illness factors, acute illness factors and health care organisational structures. We were surprised that the acute illness factors such as ICU admission illness severity and requirement for organ support had little or no influence on subsequent resource use. It is widely assumed that acute illness factors are important mediators on the causal pathway to post-critical illness morbidity, for example through residual organ dysfunction or disability.(24-26) Our data indicate that pre-illness factors, such as previous hospital resource use and comorbidity, most strongly influence subsequent hospital resource use. These findings have implications for

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clinicians, health service planners, and for future trial design where survivorship and healthcare costs beyond the acute hospital admission episode are of interest. The complex health and social care problems of ICU survivors, which in many cases may be part of a chronic trajectory of deteriorating health, justify the more holistic approach to post-ICU recovery that has been recommended by stakeholder groups(8) and the United Kingdom's National Institute for Health and Care Excellence.(27) Clinicians are increasingly aware of the burden that ICU survivorship places on patients and families. Our results will help to inform discussions with family members of the consequences of surviving an admission to ICU. In the context of recent ICU survivorship trials yielding disappointing results,(28-30) further investigation of pre-illness trajectories may identify those at highest risk of readmission and enable targeted interventions.(31)

Compared to hospital controls, we found excess hospital resource use was concentrated in younger patients and those with no previous comorbidities. These patients are most likely to be previously fit and well patients experiencing a critical illness 'hit' leaving them with new health problems.(32) This novel finding has implications for these patients, which may contrast with patients whose ICU admission punctuates an already deteriorating health trajectory. The economic consequences may be substantially greater than the costs relating to acute hospital admission, for example through substantial loss of earnings and long-term social costs. This is an important consideration for health and social policy makers, and requires confirmation in other settings.

Our population-level estimates of the cost associated with ICU survivorship can be used to inform health policy. The high emergency hospital readmission rate in ICU survivors represents unplanned access to the health service. We did not have sufficient information to classify these as potentially avoidable or unavoidable admissions in this study. Readmissions may be modifiable through proactive primary care, social care or improvement in transitions of care. Further work is required to investigate this issue.

Other studies describe excess mortality in ICU survivors compared with hospital populations, ranging from 7%(33) to 21%(34). Our data are consistent with these estimates. Comparison with other studies reporting healthcare resource use or costs is difficult due to organisational differences at ICU and wider health service level and international differences in costing healthcare.(35) However, comparing with resource data for the first year after discharge summarised in a recent systematic review and a more recent publication(35, 36), our cohort experienced comparable hospital readmission rates (1.1 compared with 0.6-2.8/patient), days in hospital (11.1 compared with 4.2-19.0/patient), though lower average one year hospitalisation ($8863 compared with $9769 to $66812 (converted to 2014 US$)).

Some studies with control populations report conflicting results to our findings. A Canadian study reported ICU survivors had a lower readmission rate compared with hospital controls during three-year follow-up (admission rate ratio 0.80, 95%CI 0.77-0.82).(37) Differences in study population (substantially younger ICU and hospital cohorts with median age 54 and 47), analysis methods (stratified analysis on vital status at the end of follow-up) and confounder selection (models included index admission hospital length of stay, strongly correlated with ICU cohort membership) may explain the discordant results. A study limited to US Medicare beneficiaries aged over 65 years found higher unadjusted one-year and three-year readmission rates in ICU survivors compared with hospital and population controls.(33) A third study of severe sepsis survivors found that, relative to other hospital survivors, patients spent a greater proportion of days alive admitted to inpatient facilities and fewer days at home in the year after hospital discharge.(38)

Strengths of our study include the use of a complete national cohort of patients, inclusion of all ICU admissions, and near complete follow-up. These factors minimise the risk of bias frequently encountered in prospective observational studies.(9) In order to investigate and fully describe the excess burden associated with ICU survivorship, we used a variety of outcomes (mortality, hospital admissions, costs), controls (hospital controls and pre-post within-individual) and multivariable

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models (negative binomial, competing risk regression) which allowed a more accurate modelling of heavily skewed resource data. As mortality rates were higher in the ICU population, our primary analysis may have demonstrated lower resource use in the ICU population due to the shorter duration of time spent alive during follow-up, although healthcare costs may also increase towards the end of life and therefore reduce this difference.(39) Our primary analysis is the correct approach from a health accounting perspective: modelling future funding of healthcare for ICU survivor populations by healthcare providers requires data relating to costs which will be lower with high, early mortality rates. However, to better understand the attributable cost of ICU survivorship, we also presented resource used by cohorts using an actuarial, life table approach, presenting mean costs per person for time intervals conditional on survival at the start of each time interval, as well as conducting additional statistical modelling to allow for the competing risk of death when comparing estimates of resource use between cohorts.

A potential weaknesses was loss of patients through emigration during follow-up; however, emigration in Scotland is known to be only 0.6% of residents aged ≥45 years annually.(17) We were also unable to identify hospital controls who 'crossed over' to become ICU survivors, thereby potentially biasing estimates away from the null. A further weakness was the method used to cost hospital resources. We used a per diem cost for each day of hospital stay which may overestimate hospital costs, particularly for hospital admissions with prolonged lengths of stay. Exposures, confounders and outcomes were also limited to those collected in registries. For example, the measure of comorbidity was likely to be imperfectly measured and there was no measure of pre-morbid functional status or frailty, which are factors that influence decision-making around ICU admission and outcomes.(40) Furthermore, data relating to limiting or withdrawing life-sustaining therapy within the ICU were not available which may have reduced the frequency of frailer individuals in the ICU cohort but not the hospital control cohort. These factors may have led to residual confounding in comparisons between ICU and hospital populations, in which the direction of bias may be away from the null if the ICU population had greater unmeasured comorbidity.

Despite matching cohorts on four variables and adjusting for available variables including pre-index admission hospital resource use, we cannot assume that hospital controls were similar to the ICU cohort in all aspects other than being admitted to ICU.(41) Because of the importance of this issue, we explored this further in the pre-post within-individual analyses of hospital readmissions. Triangulation of our observational findings using these two different approaches, each of which had their own sources of bias and confounding, demonstrated consistency in the direction of excess costs associated with ICU survivorship. Consistency in the magnitude of excess costs was more difficult to demonstrate as cost comparisons between cohorts were not controlled for imbalances between cohort characteristics other than those on which cohorts were matched.

Measurement of additional outcomes, such as functional status and quality of life, would have allowed a more complete understanding of the consequences of critical illness, but these are not available at population level. Although hospital resource dominates post-discharge costs,(35, 36) extending resource measurement beyond this to social care and societal costs, such as loss of earnings or the financial burden on carers, would have allowed a more comprehensive assessment of resource use.(42)

Conclusion

ICU survivors have increased mortality and hospital costs in the five years after ICU admission, which represents a substantial burden on individuals, carers and society. Pre-ICU admission factors indicative of poor health are strong predictors of higher long-term resource use, but excess resource use compared to other hospitalised patients is greatest for younger patients without significant pre-existing comorbidity. A better understanding of causal mechanisms, effective interventions and subgroups at higher risk is required to guide policy makers and clinicians.

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Figure legends

Figure 1. Kaplan-Meier plot of five year survival for ICU survivor cohort, hospital cohort and the general population of Scotland.

Figure 2. Hospital costs for all admission types and emergency admissions before and after index hospital admission for the ICU survivor cohort (n=5259).

Figure 3. Mean hospital costs in the five year period after discharge from index hospitalisation in ICU survivors compared with hospital controls for all patients (A) stratified by age (B: Age<70; C: Age≥70) and presence of Charlson comorbidity (D: No comorbidity; E: ≥1 comorbidity).

Figure 4. Difference in mean annual hospital costs from baseline cost in pre-post within-individual analyses in the five year period after discharge from index hospitalisation.

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Tables

	ICU cohort n=5215		Hospital control cohort n=5215		P value
	Value (SD,IQR,%)		Value (SD,IQR,%)		
Age (years) median (IQR)	60	(44, 72)	60	(44, 72)	-
Female n (%)	2327	(44.6)	2327	(44.6)	-
Scottish Index of Multiple Deprivation quintile n (%)					0.001
1 Least deprived	653	(12.5)	781	(15.0)	
2	848	(16.3)	906	(17.4)	
3	1065	(20.4)	1012	(19.4)	
4	1233	(23.6)	1179	(22.6)	
5 Most deprived	1416	(27.2)	1337	(25.6)	
Resident in remote area n (%)	471	(9.0)	542	(10.4)	0.02
Resident in rural area n (%)	916	(17.6)	905	(17.4)	0.77
Count of Charlson comorbidities n (%)					<0.001
0	3799	(72.9)	4748	(91.1)	
1	1012	(19.4)	357	(6.9)	
2 or more	404	(7.8)	110	(2.1)	
Hospital admissions in previous five years n (%)					<0.001
0	1403	(26.9)	2021	(38.8)	
1	962	(18.5)	1092	(20.9)	
2	709	(13.6)	692	(40.3)	
3	510	(9.8)	399	(7.7)	
4	347	(6.7)	292	(5.6)	
5 or more	1284	(24.7)	719	(13.8)	
Admission type n (%)					-
Elective operation	1146	(22.0)	1146	(22.0)	
Emergency operation	1447	(27.8)	1447	(27.8)	
Medical	2622	(50.3)	2622	(50.3)	
Index hospitalisation length of stay (days)					<0.001
Mean (SD)	32.5	(43.8)	11.4	(32.8)	
Median (IQR)	17	(9, 38)	3	(1, 8)	

Table 1. Baseline characteristics of ICU cohort compared with hospital control cohort. Hypothesis tests were not undertaken on variables used in matching. Note table presents data for matched

cohort n=5215; these values differ from full ICU cohort (n=5259) as 44 individuals were not matched. See eTable 1 for more detailed characteristics of the full, matched and unmatched ICU cohort.

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	Time Interval (years)	Number alive at start of interval	Mean hospital resource use during interval (mean number of admissions [upper], mean length of stay in days [lower])				Mean hospital cost accrued during interval per person alive at start of interval ($)			
			Emergency	Elective	Day case	Total (95%CI)	Emergency	Elective	Day case	Total (95%CI)
ICU cohort	0 to 1	5215	0.83 8.3	0.31 2.5	0.52 0.5	1.66 (1.57, 1.75) 11.2 (10.6, 11.9)	6317	1880	666	8863 (8332, 9393)
	1 to 2	4651	0.60 5.4	0.20 1.5	0.32 0.3	1.11 (1.04, 1.18) 7.2 (6.7, 7.8)	4116	1175	412	5704 (5269, 6138)
	2 to 3	4286	0.57 5.4	0.16 1.3	0.27 0.3	1.00 (0.93, 1.07) 6.9 (6.3, 7.5)	4104	973	342	5421 (4949, 5892)
	3 to 4	3999	0.53 5.3	0.14 1.0	0.26 0.3	0.93 (0.86, 1.00) 6.6 (5.9, 7.2)	4078	726	340	5146 (4639, 5652)
	4 to 5	3757	0.48 4.7	0.12 0.8	0.23 0.2	0.84 (0.78, 0.90) 5.8 (5.2, 6.4)	3593	628	300	4521 (4061, 4982)
	0 to 5	5215	2.58 25.0	0.82 6.2	1.39 1.4	4.79 (4.57, 5.02) 32.6 (30.9, 34.2)	19077	4738	1793	25608 (24360, 26856)
Hospital control cohort	0 to 1	5215	0.50 4.8	0.26 1.8	0.30 0.3	1.05 (0.99, 1.11) 6.9 (6.3, 7.4)	3662	1351	381	5392 (4969, 5815)
	1 to 2	4824	0.37 3.8	0.15 0.9	0.21 0.2	0.73 (0.68, 0.78) 5.0 (4.5, 5.5)	2936	698	272	3906 (3534, 4279)
	2 to 3	4558	0.33 3.4	0.13 0.8	0.18 0.2	0.65 (0.60, 0.69) 4.4 (3.9, 4.9)	2608	629	235	3473 (3098, 3848)
	3 to 4	4345	0.31 3.0	0.11 0.8	0.20 0.2	0.62 (0.57, 0.67) 3.9 (3.5, 4.4)	2268	583	255	3105 (2759, 3450)
	4 to 5	4179	0.30 2.8	0.10 0.7	0.17 0.2	0.57 (0.53, 0.61) 3.6 (3.2, 4.0)	2111	516	221	2850 (2517, 3183)
	0 to 5	5215	1.63 16.0	0.68 4.5	0.95 1.0	3.26 (3.12, 3.41) 21.5 (20.2, 22.7)	12240	3445	1227	16912 (15955, 17869)

Table 2. Mean resource use per year for ICU cohort and hospital control cohort. Mean number of admission, mean hospital length of stay, and mean cost are calculated per patient alive and under follow up at the start of each interval. 95% confidence intervals are only shown for total columns for clarity of presentation. Note this table presents resource use for matched cohorts (n=5215 per cohort); for resource use quantities for full ICU cohort (n=5259) see eTable 2.

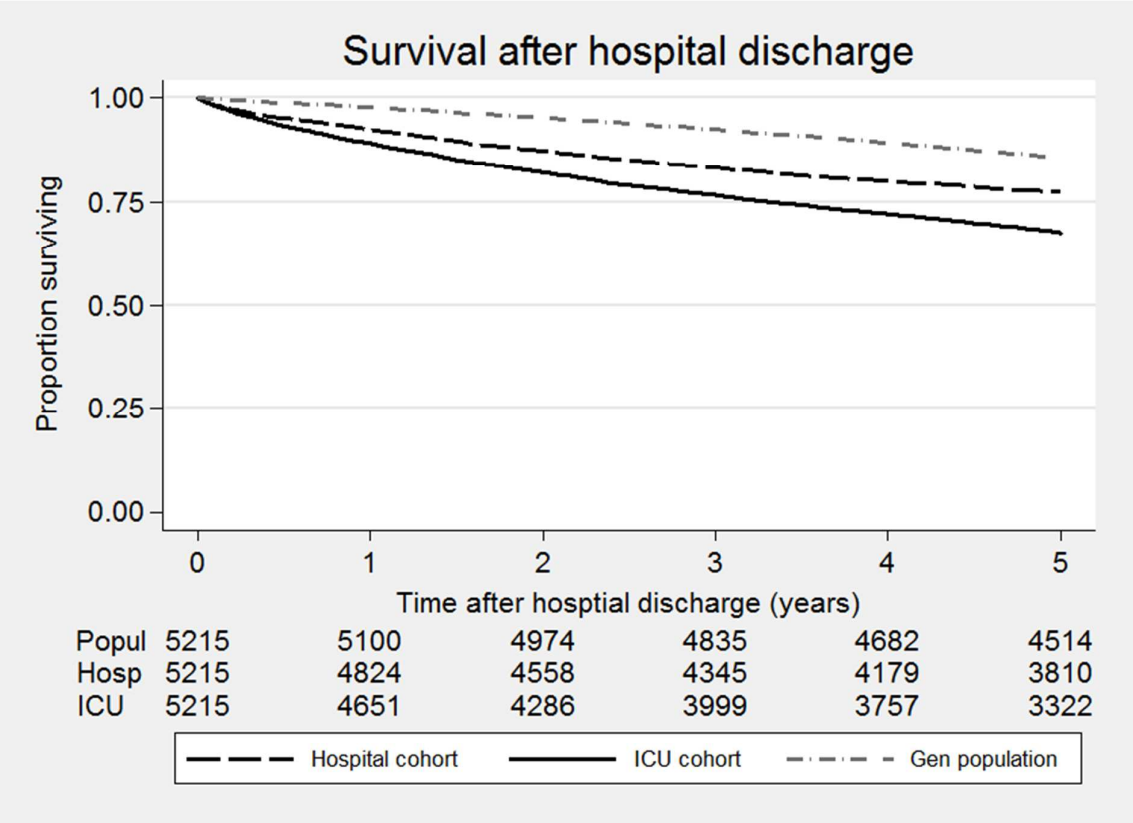

Figure 1. Kaplan-Meier plot of five year survival for ICU survivor cohort, hospital cohort and the general population of Scotland. General population mortality rates are derived using age-sex indirect standardisation. Abbreviations: 'Popul': general population at risk of event; 'Hosp': hospital control cohort at risk of event; 'ICU': ICU cohort at risk of event.

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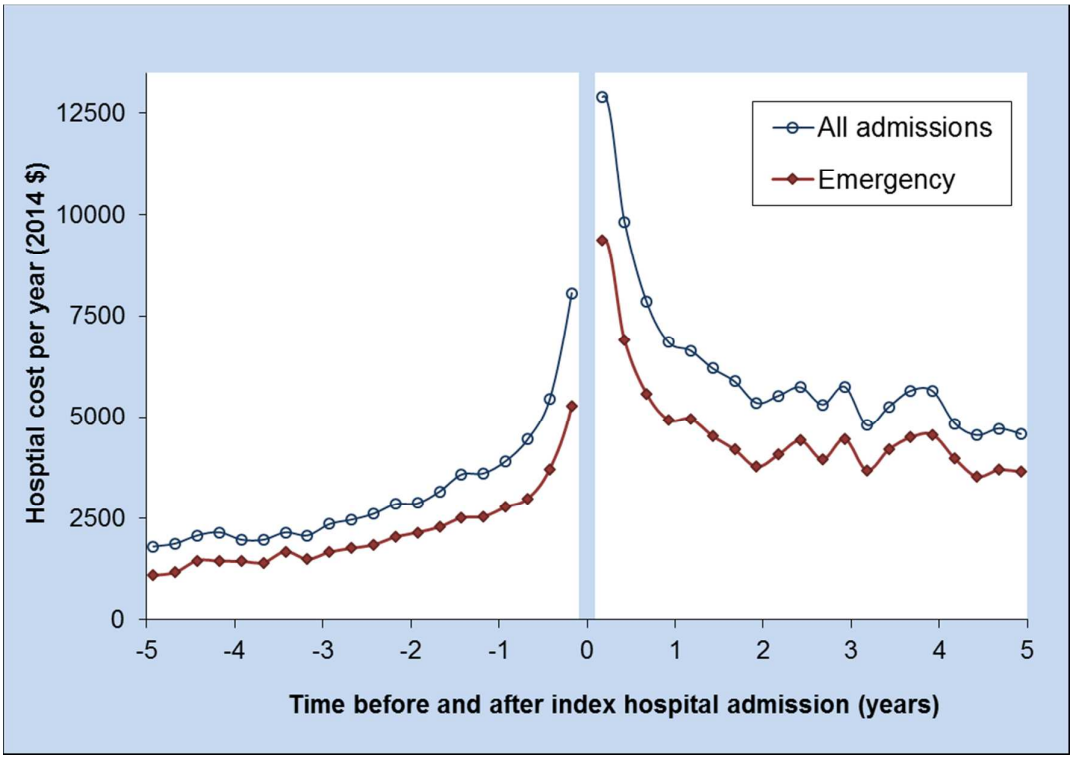

Figure 2. Hospital costs for all admission types and emergency admissions before and after index hospital admission for the ICU survivor cohort (n=5259). Each point represents the mean cost in 2014 US$ for each quarter (reported as cost per year) for each patient alive at the start of each quarter.

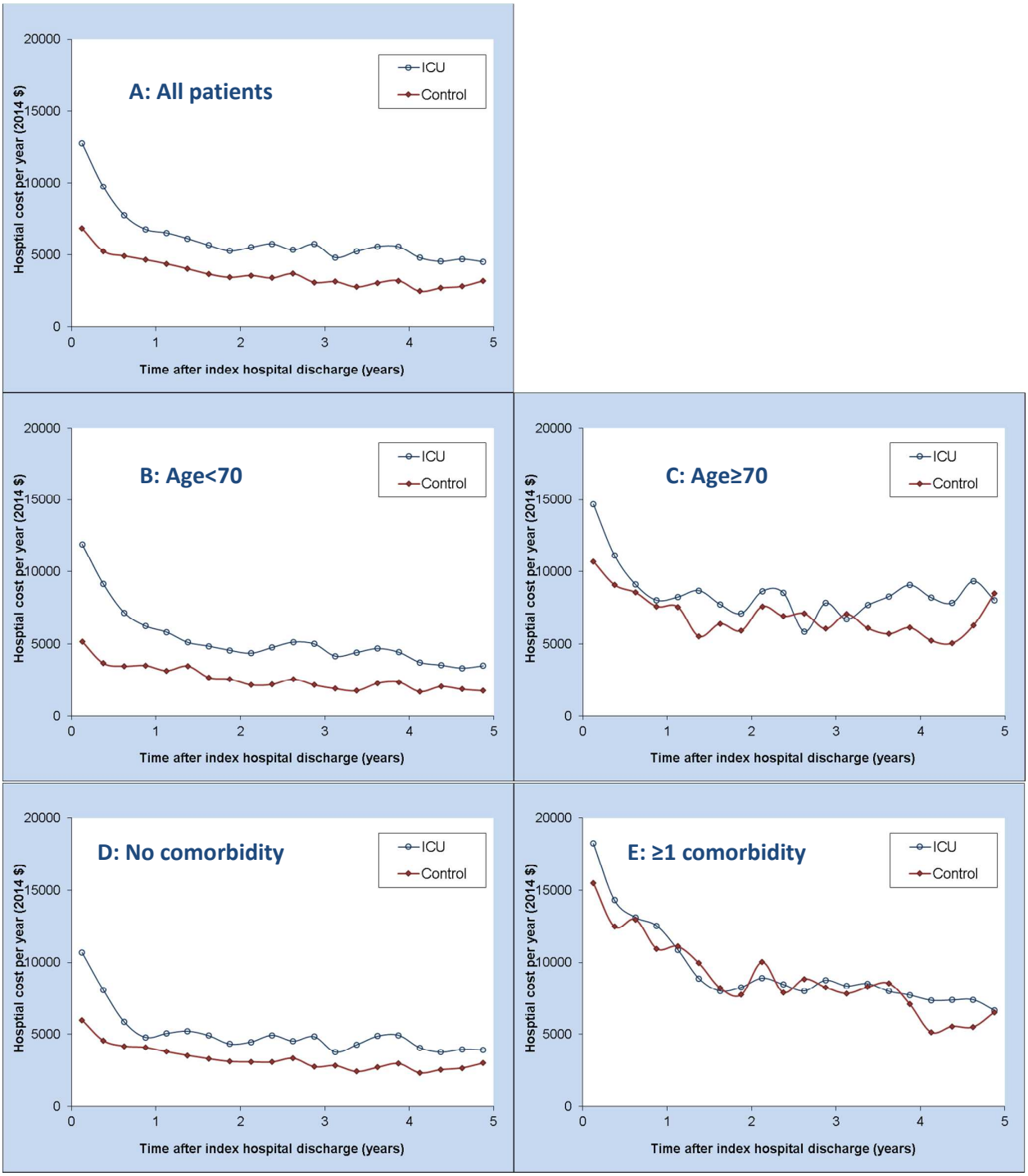

Figure 3. Mean hospital costs in the five year period after discharge from index hospitalisation in ICU survivors compared with hospital controls for all patients (A) stratified by age (B: Age<70; C: Age≥70) and presence of Charlson comorbidity (D: No comorbidity; E: ≥1 comorbidity). Each point represents the mean cost for each quarter (reported as cost per year) for each patient alive at the start of each quarter. Modelling number of admissions rather than costs, age was an effect modifier for the admission rate ratio (ARR) of ICU survivors compared with hospital controls (Age<70: ARR 1.28, 95%CI 1.18 to 1.38, p<0.001; Age≥70: ARR 1.09, 95%CI 1.00 to 1.19, p=0.05; interaction term

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p<0.001). Similarly comorbidity is an effect modifier (No comorbidity: ARR 1.25, 95%CI 1.17 to 1.34, p<0.001; 1 or more comorbidity: ARR 1.02, 95%CI 0.91 to 1.14, p=0.72; interaction term p=0.02).

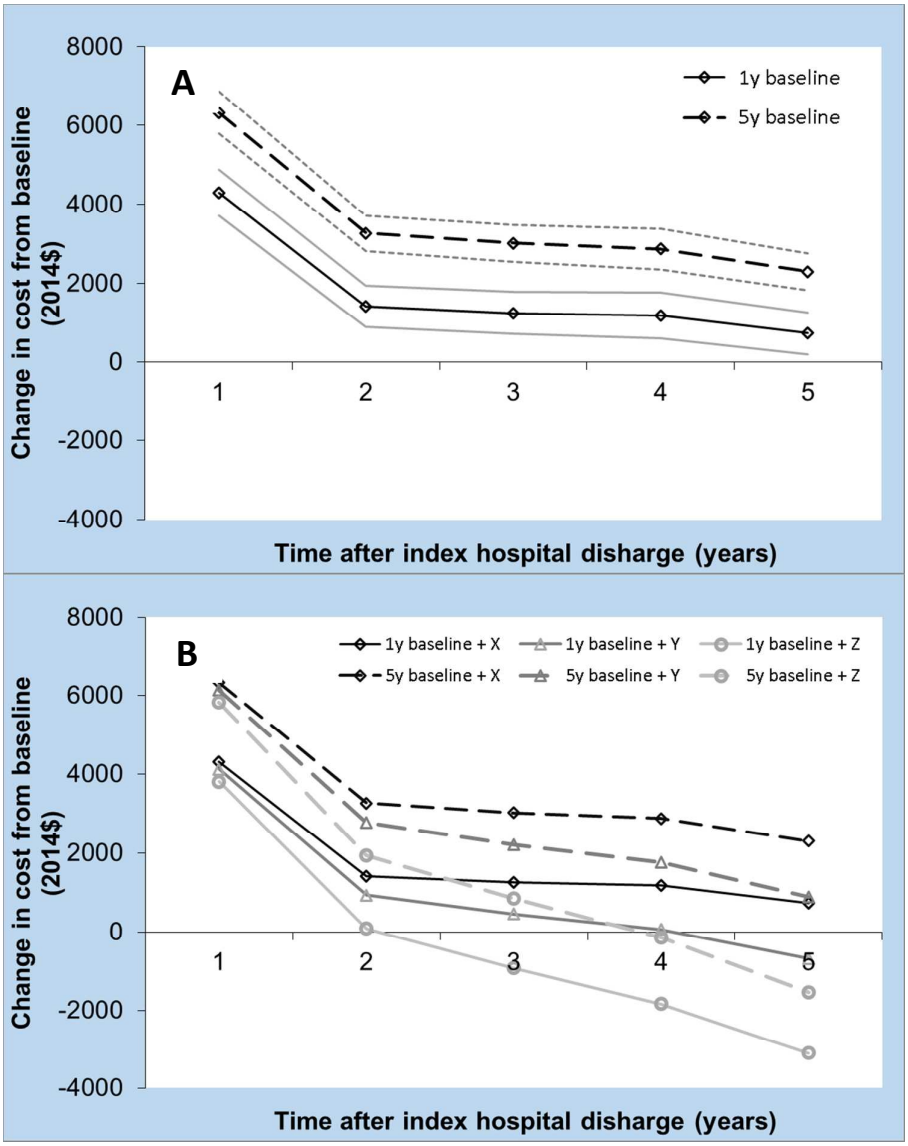

Figure 4. Difference in mean annual hospital costs from baseline cost in pre-post within-individual analyses in the five year period after discharge from index hospitalisation: sensitivity analysis in varying baseline hospital cost and effect of ageing on hospital costs. A: Baseline hospital cost was varied from the mean annual hospital cost in the one year before index hospital admission (solid) and the mean annual hospital cost in the five years before index hospital admission (dashed). 95% confidence intervals are represented by paler lines. B: In addition to varying baseline costs, the effect of ageing on hospital costs was modelled using the gradient of increasing costs during the pre-index hospitalisation period. The gradient was assumed to vary under three scenarios: no effect of ageing on costs (X); the assumption that the cost gradient during years -5, -4 and -3 pre-index hospitalisation continued during years 0 to 5 years post-hospitalisation (Y); and finally the assumption that the cost gradient from -5 years to 0 years pre-index hospitalisation continued during years 0 to 5 years post-hospitalisation (Z).

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Online Data Supplement

Five year mortality and healthcare costs associated with surviving intensive care

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Content

	Full ICU cohort n=5259		ICU cohort matched to controls n=5215		ICU cohort with no control match n=44		P value*
	Value (SD,IQR,%)		Value (SD,IQR,%)		Value (SD,IQR,%)		
Demographic characteristics							
Age (years) median (IQR)	60	(44, 72)	60	(44, 72)	46	(38, 64)	0.001
Female n (%)	2344	(44.6)	2327	(44.6)	17	(38.6)	0.42
Scottish Index of Multiple Deprivation Quintile n (%)							0.69
1 Least deprived	661	(12.6)	653	(12.5)	8	(18.2)	
2	854	(16.2)	848	(16.3)	6	(13.6)	
3	1070	(20.4)	1065	(20.4)	5	(11.4)	
4	1243	(23.6)	1233	(23.6)	10	(22.7)	
5 Most deprived	1431	(27.2)	1416	(27.2)	15	(34.1)	
Resident in remote area n (%)	470	(9.0)	470	(9.0)	0	(0.0)	0.28
Resident in rural area n (%)	919	(17.5)	914	(17.6)	5	(11.4)	0.04
Prior illness and resource use							
Count of Charlson comorbidities n (%)							0.73
0	3832	(72.9)	3799	(72.9)	33	(75.0)	
1	1020	(19.4)	1012	(19.4)	8	(18.2)	
2 or more	407	(7.7)	404	(7.8)	3	(6.8)	
Count of Charlson/SICSAG combined comorbidities n (%)							0.87
0	3438	(65.4)	3410	(65.4)	28	(63.6)	
1	1295	(24.6)	1283	(24.6)	12	(27.3)	
2 or more	526	(10.0)	522	(10.0)	4	(9.1)	
Number of hospital admissions in previous 5 years n (%)							0.53
0	1415	(26.9)	1403	(26.9)	12	(27.3)	
1	973	(18.5)	962	(18.5)	11	(25.0)	
2 or more	2871	(54.6)	2850	(54.7)	21	(47.7)	
Index admission factors							
Admission type n (%)							0.001
Elective surgery	1148	(21.8)	1146	(22.0)	2	(4.9)	
Emergency surgery	1454	(27.7)	1447	(27.8)	7	(17.1)	
Medical	2654	(50.5)	2622	(50.3)	32	(78.1)	
Admission SAPS II score median (IQR)	27	(18, 38)	27	(18, 38)	37	(26, 42)	<0.001
Mechanical ventilation n (%)	3149	(60.5)	3115	(60.3)	34	(77.3)	0.02
Renal replacement therapy n (%)	384	(7.4)	379	(7.3)	5	(11.4)	0.31
Cardiovascular support n (%)	1528	(29.4)	1511	(29.3)	17	(38.6)	0.17
ICU length of stay (days)							<0.001
Mean (SD)	5.0	(8.7)	4.9	(8.6)	12.2	(16.2)	
Median (IQR)	2	(1, 5)	2	(1, 5)	5.4	(2, 11)	
Index hospitalisation length of stay (days)							<0.001
Mean (SD)	33.9	(52.6)	32.5	(43.8)	208.0	(274.2)	
Median (IQR)	17	(9, 39)	17	(9, 38)	127	(25, 285)	

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eTable1. Baseline characteristics of whole ICU survivor cohort, those in the ICU cohort matched to hospital controls and those in the ICU cohort unmatched to hospital controls. *P values are for comparisons between members of the ICU cohort with and without matches to hospital controls (chi square test and Mann-Whitney U test). The small proportion (<1%) of the ICU cohort unmatched to hospital controls were more ill on ICU admission and had longer stays in ICU and hospital compared with those with matched controls. Abbreviations: SAPS=Simplified Acute Physiology Score; SICSAG=Scottish Intensive Care Society Audit Group. Missing data (n) were as follows for full ICU cohort: resident in remote/rural area missing n=6; admission type n=3; SAPS II score n=178; organ support three variables n=53.

Time Interval (years)	Number alive at start of interval	Mean hospital resource use during interval (mean number of admissions [upper], mean length of stay in days [lower])				Mean hospital cost accrued during interval per person alive at start of interval ($)			
		Emergency	Elective	Day case	Total (95% CI)	Emergency	Elective	Day case	Total (95%CI)
0 to 1	5259	0.83 8.4	0.31 2.5	0.52 0.5	1.66 (1.57,1.74) 11.4 (10.7, 12.1)	6422	1880	663	8967 (8427, 9507)
1 to 2	4688	0.6 5.5	0.2 1.6	0.32 0.3	1.12 (1.05, 1.19) 7.4 (6.8, 8.0)	4234	1191	411	5838 (5391, 6284)
2 to 3	4317	0.58 5.4	0.16 1.3	0.26 0.3	1.01 (0.93, 1.08) 6.9 (6.3, 7.5)	4110	976	341	5428 (4960, 5896)
3 to 4	4027	0.53 5.4	0.14 1.0	0.26 0.3	0.94 (0.87, 1.01) 6.6 (6.0, 7.3)	4127	730	341	5199 (4696, 5702)
4 to 5	3780	0.49 4.7	0.12 0.8	0.23 0.2	0.85 (0.78, 0.91) 5.8 (5.2, 6.4)	3625	628	300	4554 (4091, 5016)
0 to 5	5259	2.60 22.4	0.82 5.5	1.39 1.4	4.81 (4.44, 5.00) 29.2 (26.1, 29.7)	19340	4755	1787	25881 (24608, 27153)

eTable 2. Mean annual and five year hospital resource use for the ICU survivor cohort (n=5259). Mean number of admissions, mean hospital length of stay, and mean cost are calculated per patient alive and not lost to follow up at the start of each interval. 95% confidence intervals are only shown for total columns for clarity of presentation.

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	Negative binomial regression; outcome: number of admissions over 5 year follow-up						Fine and Gray regression: outcome: cumulative incidence of first admission					
	Adm RR	95% CI Lower	Upper	Wald X^2	df	p value	Sub HR	95% CI Lower	Upper	Wald X^2	df	p value
Demographics												
Age				18.8	3	<0.001				19.6	3	<0.001
16-43	Ref						Ref					
44-59	1.14	1.04	1.25				1.24	1.12	1.36			
60-71	1.03	0.93	1.14				1.12	1.01	1.25			
72-101	0.93	0.84	1.04				1.15	1.03	1.29			
Female (ref male)	0.99	0.93	1.06	0.1	1	0.75	1.01	0.95	1.07	0.1	1	0.80
SIMD quintile				17.1	4	0.002				9.6	4	0.05
1 Least deprived	Ref						Ref					
2	1.04	0.92	1.17				1.14	1.01	1.29			
3	1.22	1.09	1.37				1.18	1.05	1.33			
4	1.15	1.03	1.29				1.14	1.02	1.27			
5 Most deprived	1.15	1.03	1.28				1.17	1.05	1.30			
Remote	0.97	0.86	1.10	0.2	1	0.68	0.97	0.87	1.09	0.2	1	0.63
Rural	0.93	0.85	1.02	2.2	1	0.13	0.99	0.90	1.08	0.1	1	0.76
Prior illness and resource use												
Hospital adm in prev 5 yrs	1.05	1.04	1.05	241.3	1	<0.001	1.02	1.01	1.02	51.1	1	<0.001
Charlson/SICSAG comorbidities				77.6	3	<0.001				98.3	3	<0.001
0	Ref						Ref					
1	1.39	1.29	1.51				1.35	1.25	1.46			
2	1.37	1.21	1.55				1.55	1.36	1.76			
3 or more	1.25	1.03	1.51				1.70	1.42	2.03			
Index admission factors												
Admission type				11.0	2	0.004				3.6	2	0.16
Elective surgery	Ref						Ref					
Emergency surgery	0.89	0.79	0.99				0.93	0.83	1.04			
Medical	0.82	0.73	0.92				0.89	0.80	1.00			
Prior CPR	0.94	0.73	1.22	0.2	1	0.65	1.24	0.95	1.63	2.5	1	0.12
Diagnosis on ICU adm				110.9	27	<0.001				103.1	27	<0.001
28 categories												
SAPS II score (per 10pt)	1.04	1.01	1.07	5.2	1	0.02	1.01	0.98	1.04	0.3	1	0.58
Mechanical ventilation	0.91	0.85	0.99	5.4	1	0.02	0.96	0.89	1.03	1.4	1	0.23
Renal replacement	1.10	0.96	1.25	1.9	1	0.17	1.05	0.92	1.20	0.5	1	0.50
Cardiovascular support	1.04	0.96	1.13	0.9	1	0.35	1.07	0.99	1.16	3.1	1	0.08

eTable 3a. Factors associated with hospital resource use for the ICU survivor cohort (n=5259). Negative binomial regression was used to identify predictors of resource use measured as 'number of admissions during five year follow up'. Fine and Gray competing risks regression was used to identify predictors of resource use measured by the sub-distribution hazard rate allowing for the competing risk of death. Where differences exist in estimates for covariates between the two models, this is either related to differences in mortality rates (higher, early mortality rates tends to reduce admission rate ratios but not subhazard ratios) or a difference in relationship between the two outcomes being modelled (total number of readmissions in negative binomial model; cumulative incidence of first readmission in Fine and Gray model). Diagnosis on ICU admission is expanded in eTable 3b. Abbreviations: Adm RR=admission rate ratio; CPR=cardiopulmonary resuscitation; ref=reference category; SAPS=Simplified Acute Physiology Score; SICSAG=Scottish Intensive Care Society Audit Group; SIMD=Scottish Index of Multiple Deprivation; Sub HR=sub-distribution hazard ratio.

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		n (%)	Negative binomial regression; outcome: num of admissions over 5 year follow-up				Fine and Gray regression: outcome: cumulative incidence of first admission			
			AdmRR	95% CI Lower	95% CI Upper	p value	SubHR	95% CI Lower	95% CI Upper	p value
	Trauma excluding head injury	309 (5.9)	1	Ref			1	Ref		
CVS	Post-cardiac arrest	87 (1.7)	0.97	0.72	1.29	0.81	1.15	0.86	1.54	0.33
	Cardiogenic shock	17 (0.3)	1.03	0.58	1.82	0.93	1.22	0.75	1.97	0.42
	Septic shock	256 (4.9)	1.23	1.00	1.50	0.05	1.32	1.07	1.63	0.01
	AAA rupture	67 (1.3)	1.15	0.83	1.58	0.40	0.99	0.74	1.33	0.97
	Vascular surgery	224 (4.3)	1.15	0.93	1.42	0.19	1.10	0.90	1.35	0.36
Resp	Pneumonia	461 (8.8)	1.42	1.18	1.71	<0.001	1.29	1.08	1.54	0.01
	ARDS	29 (0.6)	1.45	0.94	2.26	0.10	1.48	0.90	2.45	0.13
	Asthma	90 (1.7)	1.81	1.37	2.39	<0.001	1.39	1.07	1.81	0.01
	COPD	64 (1.2)	2.16	1.59	2.95	<0.001	1.41	1.08	1.84	0.01
Liver/GI	Acute GI pathology*	428 (8.1)	1.50	1.25	1.80	<0.001	1.54	1.29	1.84	<0.001
	GI bleed	155 (3.0)	1.28	1.02	1.61	0.03	1.55	1.23	1.95	<0.001
	GI neoplasm	265 (5.0)	1.56	1.27	1.92	<0.001	1.46	1.18	1.79	<0.001
	GI obstruction	253 (4.8)	1.69	1.39	2.06	<0.001	1.51	1.24	1.84	<0.001
	Liver failure	26 (0.5)	1.63	1.03	2.60	0.04	1.81	1.22	2.69	0.003
	Oesophageal variceal bleed	51 (1.0)	2.26	1.63	3.14	<0.001	2.67	1.92	3.71	<0.001
	Pancreatitis	75 (1.4)	1.58	1.18	2.12	0.002	1.67	1.22	2.28	0.001
CNS	Seizures	146 (2.8)	1.53	1.21	1.94	<0.001	1.43	1.13	1.82	0.003
	Intracranial bleed	75 (1.4)	1.24	0.92	1.67	0.16	1.44	1.05	1.97	0.02
Other	Diabetic ketoacidosis	43 (0.8)	0.96	0.65	1.40	0.82	1.27	0.87	1.84	0.22
	Trauma including head injury	134 (2.6)	1.03	0.80	1.32	0.83	1.06	0.81	1.37	0.68
	Self poisoning	287 (5.5)	1.47	1.19	1.80	<0.001	1.09	0.89	1.33	0.42
	Other CVS	179 (3.4)	1.13	0.91	1.41	0.28	1.34	1.08	1.66	0.01
	Other respiratory	357 (6.8)	1.28	1.06	1.55	0.01	1.49	1.23	1.80	<0.001
	Other GI	334 (6.4)	1.44	1.20	1.74	<0.001	1.38	1.15	1.66	0.001
	Other renal	161 (3.1)	1.27	1.01	1.59	0.04	1.46	1.17	1.83	0.001
	Other CNS	185 (3.5)	0.98	0.78	1.23	0.85	1.04	0.82	1.32	0.74
	Other miscellaneous†	501 (9.5)	1.30	1.09	1.56	0.004	1.11	0.92	1.33	0.28

eTable 3b. Factors associated with hospital resource use for the ICU survivor cohort (n=5259). Expansion from eTable 3a. *Acute GI pathology includes the following diagnoses: GI perforation, abscess, diverticulitis, peritonitis, and ischaemia. †The missing category was combined with 'other miscellaneous' for analyses. Abbreviations: AAA=abdominal aortic aneurysm rupture; AdmRR=admission rate ratio; ARDS=acute respiratory distress syndrome; COPD=chronic obstructive pulmonary disease; CNS=central nervous system; CVS=cardiovascular system; GI=gastrointestinal; ref=reference category; Sub HR=sub-distribution hazard ratio.

	Negative binomial regression; outcome: number of admissions over 5 year follow-up						Fine and Gray regression: outcome: cumulative incidence of first admission					
	AdmRR	95% CI		Wald X^2	df	p value	SubHR	95% CI		Wald X^2	df	p value
		Lower	Upper					Lower	Upper			
SAPS II (per 10 point increase)	1.04	1.01	1.07	6.6	1	0.01	1.01	0.98	1.04	0.9	1	0.36
Renal replacement therapy	1.15	1.02	1.31	5.1	1	0.02	1.08	0.96	1.23	1.5	1	0.21
Mechanical ventilation	0.96	0.89	1.03	1.6	1	0.21	0.99	0.92	1.05	0.2	1	0.67
Cardiovascular support	1.05	0.97	1.13	1.3	1	0.25	1.08	1.00	1.16	3.8	1	0.05
Maximum number of organs supported				0.3	3	0.97				1.2	3	0.76
0	Ref						Ref					
1	0.99	0.92	1.06				0.98	0.91	1.06			
2	1.01	0.91	1.11				1.03	0.93	1.13			
3	1.01	0.80	1.27				1.06	0.85	1.32			
ICU length of stay (days)				2.4	3	0.49				1.2	3	0.75
0	Ref						Ref					
1	1.05	0.93	1.18				1.01	0.90	1.14			
2-4	1.08	0.96	1.22				1.05	0.93	1.18			
5+	1.09	0.96	1.24				1.02	0.90	1.16			
Hospital length of stay (days)				28.4	3	<0.001				42.1	3	<0.001
0-8	Ref						Ref					
9-16	1.20	1.08	1.32				1.20	1.09	1.32			
17-38	1.30	1.18	1.44				1.31	1.19	1.45			
39+	1.21	1.10	1.34				1.38	1.25	1.53			
Post-ICU length of stay (days)				11.8	3	0.01				38.8	3	<0.001
0-5	Ref						Ref					
6-11	1.10	1.00	1.21				1.18	1.07	1.29			
12-27	1.18	1.07	1.29				1.29	1.17	1.42			
28+	1.13	1.03	1.25				1.36	1.23	1.51			

eTable 4. Markers of severity of illness in ICU and length of stay: multivariable association with count of hospital admissions over five years using negative binomial regression and time to first readmission within five years of hospital discharge allowing for the competing risk of death using Fine and Gray regression. Note in multivariable analyses, due to collinearity each of the 8 covariates was entered individually in multivariable models containing other potential predictors (age, sex, deprivation, combined comorbidity, number of previous admissions, prior CPR, ICU admission diagnosis, remoteness, rurality, admission type). Therefore, the AdmRR/SubHR reported is adjusted for these predictors but not the remaining 7 variables listed in the table. Abbreviations: AdmRR=admission rate ratio; ref=reference category; SAPS=Simplified Acute Physiology Score; Sub HR=sub-distribution hazard ratio.

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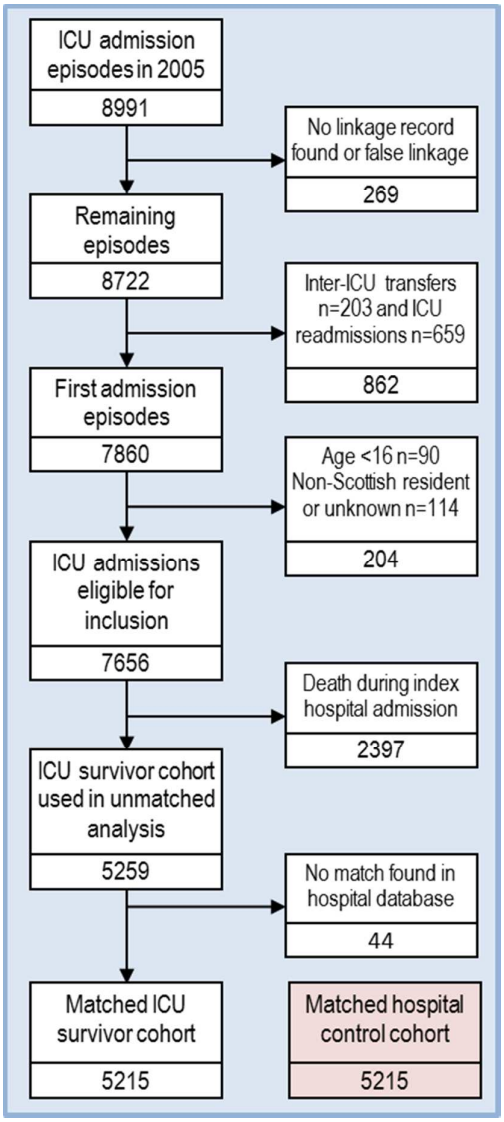
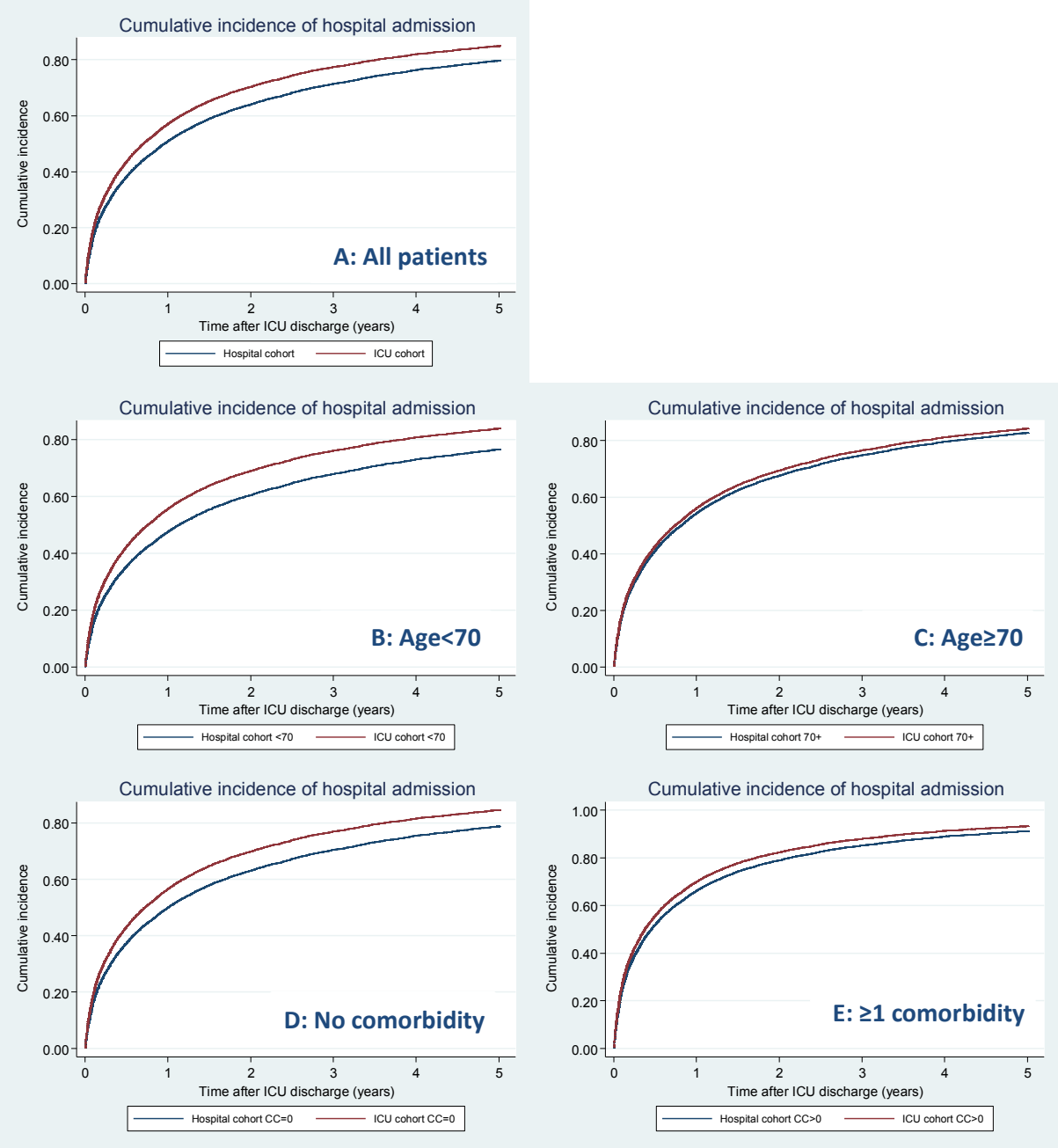
2. Online only figures



eFigure 1. Flowchart describing derivation of ICU cohort.



eFigure 2. Predicted cumulative incidence proportion (%) of first hospital readmission comparing ICU survivor and hospital control cohorts for all patients (A) stratified by age (B: Age<70; C: Age≥70) and presence of comorbidity (D: No comorbidity; E: ≥1 comorbidity). Graphs are plotted at the median/mode value of the remaining predictor variables. Age was an effect modifier for the sub-distribution hazard ratio (SubHR) of ICU survivors compared with hospital controls (Age<70: SubHR 1.23, 95%CI 1.16 to 1.30, p<0.001; Age≥70: SubHR 1.10, 95%CI 1.01 to 1.19, p=0.02; interaction term p<0.001). In contrast, comorbidity was not a significant effect modifier (No comorbidity: SubHR 1.19, 95%CI 1.13 to 1.25, p<0.001; 1 or more comorbidity: SubHR 1.07, 95%CI 0.95 to 1.20, p=0.26; interaction term p=0.26). 37% of the population with ≥1 comorbidity were aged ≥70; 22% of those aged ≥70 had ≥1 comorbidity.

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3. Supplementary Methods

Setting

There were 24 general intensive care units (ICUs) in Scotland during 2005, of which six admitted both level three and level two patients to combined units.[1] Only a few critical care services are not provided within Scotland, for example extracorporeal membrane oxygenation and lung transplantation.

Databases

The primary data sources were routinely collected, administrative health care registry databases. Registries were linked using probabilistic matching methods by Information Services Division (ISD). Manual checking of linkages indicates that the accuracy of this method of data linkage is high.[2]

Intensive care registry: The SICSAG registry contains records relating to all admissions to general ICUs and combined ICU/HDUs in Scotland. Most data are collected prospectively at the time of admission by clinical staff in the ICU. However, data relating to which organs are being supported are entered on a daily basis during the ICU stay. Quality assessment is undertaken using point of entry validation, case note validation and central validation.[1] Case note validation is taken on a random sample of 5% of ICU admissions with only a 6% disagreement.[1]

Hospital discharge registry: Scottish Morbidity Record 01 (SMR01) is the name of the registry containing data on all non-psychiatric, non-obstetric acute hospital inpatient and day case (elective admissions not requiring an overnight stay in hospital) discharges in Scotland.

Death records registry: All deaths in Scotland must be legally registered with National Records Scotland (NRS). Death data have been routinely linked to the Scottish health care registries since 1981. The quality of data in the NRS registry is of a high standard.[3]

Variables

Patient characteristics were derived from both the SMR01 and SICSAG registries. However, for matched analyses, only variables recorded in the SMR01 registry could be used in analyses as information relating to the hospital cohort was derived from the SMR01 registry exclusively.

SMR01 variables: age, social deprivation, remoteness, rurality, Charlson comorbidities, admission type (emergency surgical, elective surgical, medical), previous resource use, health board of residence, length of hospital stay.

SICSAG variables: diagnosis on admission to ICU, SAPS II (severity of illness) score, prior cardiopulmonary resuscitation, daily organ support data (mechanical ventilation, renal replacement therapy, vasoactive therapy, maximum number of organs supported), length of ICU stay, post-ICU hospital length of stay, combined Charlson and SICSAG comorbidities.

Age: After checking linearity, age was entered as a continuous variable in matched models with mortality as the outcome despite matching on age-bands between ICU and hospital cohorts. This was to remove the residual confounding relating to age within the age bands. For all analyses in which resource use was the outcome (matched and unmatched, negative binomial and Fine and

Gray models), age was entered as a categorical term based on quartiles of age in the survivor cohort (16-43, 44-59, 60-71, 72-101) as age did not have a linear relationship with the outcome.

Demographic characteristics: Socioeconomic status was measured using the Scottish Index of Multiple Deprivation (SIMD) 2009.[4] SIMD is an area-based ranking measure of relative deprivation across Scotland and was used in analyses as quintiles. Remoteness and rurality are defined by the Scottish Office of National Statistics and were used in analyses as binary variables.[5] A rural settlement is defined as one with fewer than 3000 people. A remote settlement is defined as one containing fewer than 10,000 people with a drive time of greater than 30 minutes to the nearest settlement with 10,000 or more people in it. Health region of residence was potentially disclosive and so small regions were combined to give eleven categories.

Diagnosis on admission to ICU: Diagnosis on admission was derived primarily from APACHE III and SICSAG diagnostic coding system. The number of diagnostic categories needed to be reduced for entry into regression models. The final diagnostic categories were selected to be recognised diseases or clinical syndromes of sufficient size for analyses. Two independent clinicians combined similar diagnostic categories or those with small frequencies into 'other' categories to produce 28 categories. A third ICU clinician reviewed differences in the coding method and had the final decision in deciding which categories would be combined. Missing diagnoses were classified as 'other'.

Measures of comorbidity: There were two separate measures of comorbidity derived from the registries: the Charlson list of comorbidities derived from previous hospital admissions recorded in SMR01; and the comorbidities recorded in the SICSAG registry as part of severity of illness scoring. The 17 comorbidities identified by Charlson were derived from a one year 'look-back' period from the date of the hospital admission during which the index ICU admission occurred using published ICD coding algorithms.[6] The comorbidities extracted from the SICSAG database were derived from those recorded at the time of ICU admission by health care staff as part of the APACHE II and the SAPS II comorbidities. This resulted in six comorbidity categories derived from the SICSSAG database: severe cardiovascular disease, severe respiratory disease, severe liver disease, end stage renal disease, immunosuppression and metastatic cancer. In order to maximise use of the two separate measures of comorbidity and reduce duplication of these measures, we combined the 23 categories to produce 20 comorbid categories. The 20 combined Charlson and SICSAG comorbidities were entered as a count of comorbidities (0, 1, 2, ≥3) in unmatched regression models. The 17 Charlson comorbid categories were entered as a count of comorbidities (0, 1, 2, ≥3) in regression models in matched analyses as only Charlson comorbidities were available in the hospital SMR01 database.

Previous resource use: The number of admissions to acute hospitals during the five year period prior to the date of the hospital admission during which the index ICU admission occurred was used as a measure of previous health care resource use. It was entered as a continuous term after assessing for linearity.

Length of stay variables: Length of stay variables were categorised into quartiles and entered as categorical terms in models due to having non-linear relationships with the outcome. Post-ICU hospital length of stay was derived by subtracting the ICU discharge date from the hospital discharge date.

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Severity of illness scores: SAPS II score was entered in all models as a continuous variable after assessing linearity.

Organ support data: Receipt of organ support was categorised into a binary variable for each organ system: invasive mechanical ventilation, renal replacement therapy and vasoactive therapy. The maximum number of organs supported measured cumulatively rather than simultaneously. For example, a patient classified as receiving support for three organs could in theory have had cardiovascular support alone on day 1, renal replacement therapy alone on day 2 and mechanical ventilation alone on day 3.

Variable selection

Non-matched analyses: We undertook multivariable analyses restricted to the ICU cohort to identify independent predictors of resource use. We assessed the following variables in models: 1. demographic factors: age, sex, social deprivation quintile, remoteness, rurality; 2. prior illness/resource use factors: number of hospital admissions in the previous five years, number of combined SICSAG and Charlson comorbidities; and 3. acute illness factors: prior cardiopulmonary resuscitation, admission type, ICU admission diagnosis, SAPS II score, receipt of organ support (invasive mechanical ventilation, renal replacement therapy and vasoactive therapy as individual variables).

In order to better elucidate the association between eight acute illness-related factors and outcome and to reduce problems associated with collinearity, we constructed a baseline model with the variables listed above but removed variables relating to illness severity (SAPS II score and organ support). We assessed the relationship between each of the eight variables (SAPS II score, renal replacement therapy, mechanical ventilation, cardiovascular support, maximum number of organs supported, ICU length of stay, hospital length of stay and post-ICU hospital length of stay) with the outcome by entering the variable into the baseline model (eTable 4).

Matched analyses: Comparisons of outcomes for ICU and hospital control cohorts were adjusted for the following confounders: age, social deprivation quintile, remoteness, rurality, health region of residence, number of hospital admissions in the previous five years, and number of Charlson comorbidities. Length of hospital stay was not included in models as we decided *a priori* that this was likely to, in part, act as a mediator for the association between the exposure (ICU vs hospital) and the outcome. Empirical testing revealed the hospital length of stay was strongly correlated with ICU vs hospital cohort membership (Spearman's rho 0.55, $p<0.0001$).

Sample size

For mortality, the sample size (n=10430) was sufficient to detect a statistically significant hazard ratio <0.91 or >1.11 using a Cox model (assumptions: $\alpha=0.05$, $\beta=0.2$, mortality probability 0.33 in ICU cohort). If 50% of the variance of the Cox model was explained by confounding covariates, the hazard ratio limits widened (<0.87; >1.14).

Statistical analysis

We used a significance level of 5% and 95% confidence intervals (CI). CIs for admission rate ratios were calculated assuming a negative binomial distribution with robust standard errors.[7]Bootstrap CIs for the mean of resource outcomes were estimated drawing 10000 samples with replacement.

All p values were two-sided. We used the following statistical tests for matched analyses: McNemar's chi-square; Wilcoxon signed rank test; conditional logistic regression for categorical variables.

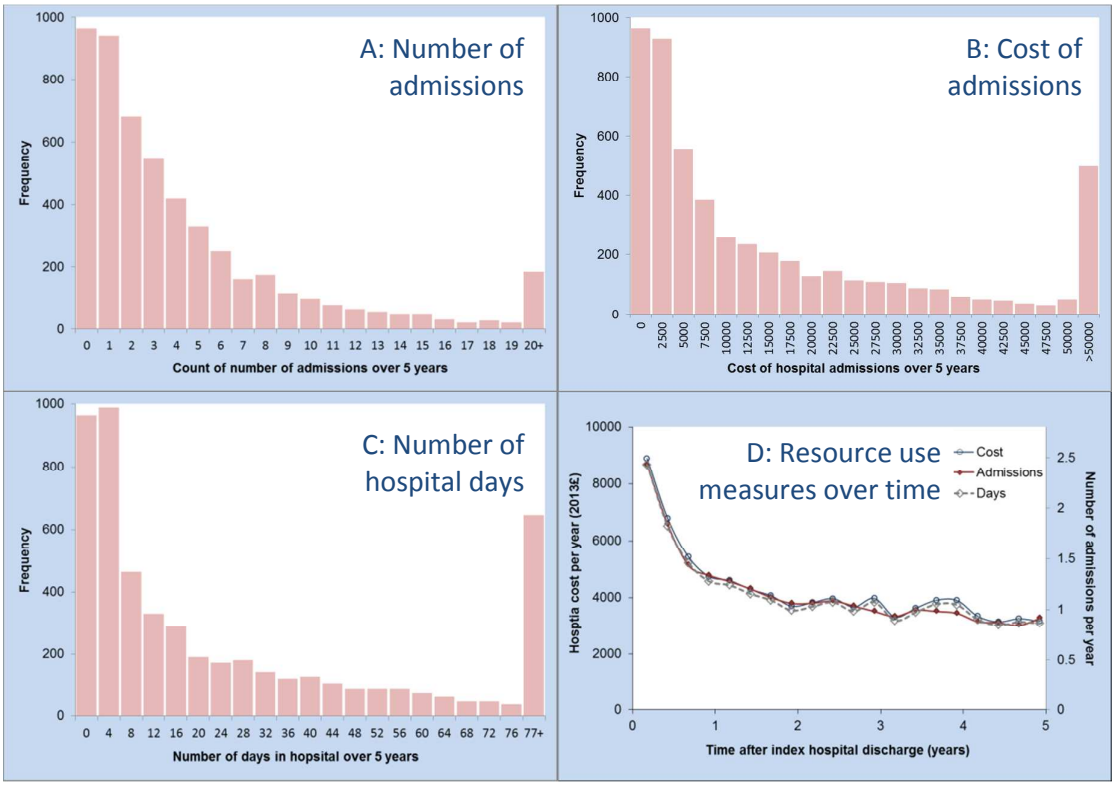
Statistical modelling

Mortality

Cox regression stratified by matched pairs was used to estimate the hazard ratio for the comparison of mortality for the ICU compared with hospital cohort. The proportional hazards assumption was assessed using log-minus-log plots of estimated survival probability and Schoenfeld residuals.

Resource use

Count models: The three resource outcome measures had similar distributions (number of admissions (eMethods Figure 1.A), cost of admissions (eMethods Figure 1.B), and number of days in hospital (eMethods Figure 1.C). Modelling resource use as a dependent variable was problematic due to the shape of the distribution: a high frequency of zero values and a long tail of low frequency higher values. Logarithmic transformation was unhelpful due to log(0) creating missing values. A number of count data models can potentially accommodate this distribution. We, therefore, chose to model number of admissions during five years as the resource use dependent variable which displayed a similar frequency over time to hospital costs (eMethods Figure1).



eMethods Figure 1. Comparison of frequencies of resource use outcomes (A, B and C) and resource use outcomes over time (D). In Figures A-C the leftmost bar indicates the frequency of 'zero' values

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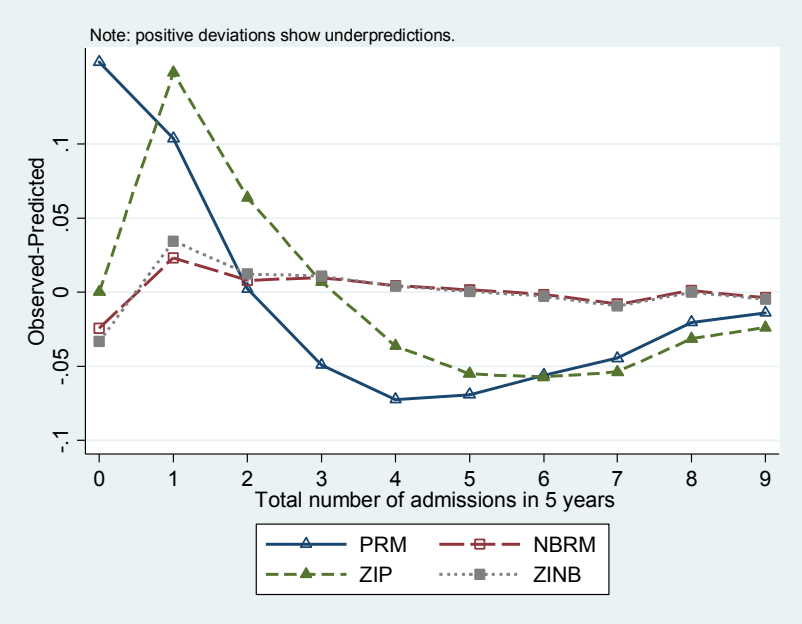
only. Note that in Figure D the y-axis values for number of hospital days has not been plotted due to limitations of space. Its axis scale is 0 to 20.

In order to select the most appropriate count data regression model, we compared the negative binomial model to other count regression models using the 'countfit' command in Stata.[8] We compared observed and predicted probabilities of number of admissions and well as model fit using Bayesian Information Criterion (BIC). This demonstrated that the negative binomial model provided the best fit for the data (eMethods Figure 2, eMethods Table 2). The exponentiated coefficients produced by this regression model can be interpreted as admission rate ratios. In comparison with the Poisson model, the negative binomial model allows for overdispersion in count data (variance>mean rather than variance=mean)[9] and also allows for differing propensities that individual patients might have of experiencing recurrent hospital admissions, so that a patient admitted to hospital once may have an increased chance of being readmitted subsequently during the five years (contagion). In contrast, the Poisson distribution assumes a constant event rate over time and assumes intra-individual independence of observations.[7,9] The negative binomial model also allows for an increased number of zero counts,[7] and has an advantage over zero-inflated count models in having fewer parameters.



eMethods Figure 2. Plot of observed-predicted outcomes against total number of admissions to compare performance of four count regression models: PRM=Poisson regression model; NBRM=Negative binomial regression model; ZIP=Zero-inflated Poisson regression model; ZINB=Zero-inflated negative binomial regression model. If a model perfectly predicted the outcome, the plotted line would be horizontal and cross the y-axis at zero. Positive deviations indicate underprediction; negative deviations indicate over prediction. The negative binomial regression model best predicts the outcome using this criterion.

Regression model	BIC
Negative binomial	26396
Zero-inflated negative binomial	26671
Zero-inflated Poisson	39926
Poisson	43328

eMethods Table 1. Comparing model fit of four count regression models using Bayesian Information Criterion (BIC). A lower BIC value indicates a better model fit.

Pre-post within-individuals cost analysis: Difference in mean annual post-index discharge hospital costs from baseline hospital costs was calculated for each individual patient. Baseline hospital costs represented the hypothetical scenario of the cost of hospital resource use for an individual in the years after index hospital discharge had they not been admitted to ICU during their index hospitalisation.

We used an individual patient's hospital costs accrued during the five years pre-index hospital admission to estimate baseline hospital costs. We varied two aspects of costs: (1) the timeframe over which mean annual hospital cost was derived and (2) the effect of ageing on costs.

(1) The timeframe over which mean annual hospital cost was derived was varied between two extremes: one year before index hospital admission and five years before index hospital admission. It is likely that some costs in the year before ICU admission are causally related to the acute episode of critical illness, and this may therefore overestimate baseline hospital costs. Using a five year period to derive baseline costs helps to reduce the magnitude of this problem.

(2) Increasing age is likely to be associated with increased hospital costs. To allow for the effect of ageing on baseline hospital costs over the five year follow up period, we used the gradient of increasing costs during the pre-index hospitalisation period to model this. The gradient was assumed to be linear and to vary under three scenarios: no effect of ageing on costs; the assumption that the cost gradient during years -5, -4 and -3 pre-index hospitalisation continued during years 0 to 5 years post-hospitalisation; and finally the assumption that the cost gradient from -5 years to 0 years pre-index hospitalisation continued during years 0 to 5 years post-hospitalisation. The third scenario may overestimate baseline costs as it includes the immediate pre-ICU period during which costs may be casually related to the acute episode of critical illness.

Combining these two aspects gave rise to six possible scenarios for baseline costs (eMethods Table 2; eMethods Figure 3): For simplicity, no allowance was made for discounting or inflation.

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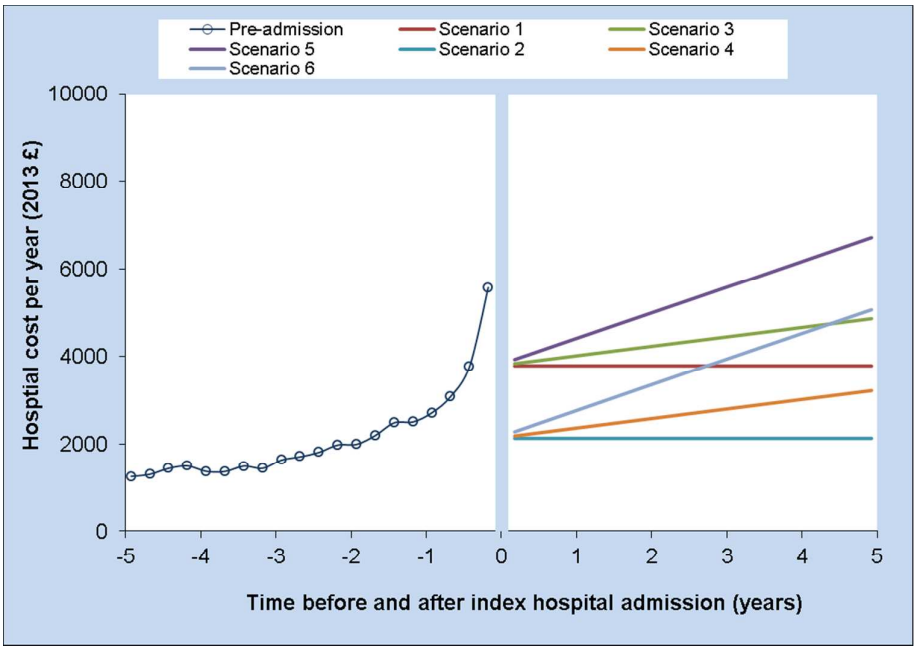
Scenario	Mean annual hospital cost	Effect of ageing
1	1 year pre-index hospitalisation	Zero
2	1 year pre-index hospitalisation	Years -5 to -3
3	1 year pre-index hospitalisation	Years -5 to -1
4	5 year pre-index hospitalisation	Zero
5	5 year pre-index hospitalisation	Years -5 to -3
6	5 year pre-index hospitalisation	Years -5 to -1

eMethods Table 2. Derivation of baseline annual hospital cost estimates under 6 scenarios. See text for details.



eMethods Figure 3. Estimating baseline hospital costs in the five years after index hospital discharge. Mean annual pre-admission costs were derived empirically and plotted at 3-monthly intervals. Baseline costs for the five years after index hospital discharge were estimated under 6 scenarios by varying two factors: mean annual hospital cost and the effect of ageing on annual costs. Scenarios 1-3 (*mean annual hospital cost* from 1 year pre-index hospitalisation; *ageing effect* gradient zero, years -5 to -3, years -5 to -1) and Scenarios 4-6 (*mean annual hospital cost* from 5 years pre-index hospitalisation; *ageing effect* gradient zero, years -5 to -3, years -5 to -1). See eMethods Table 2 for details.

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