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Factors influencing early and late readmissions in Australian hospitalised patients and investigating role of admission nutrition status as a predictor of hospital readmissions: a cohort study

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Abstract

Objectives: Limited studies have identified predictors of early and late hospital readmissions in Australian healthcare settings. Some of these predictors may be modifiable through targeted interventions. A recent study has identified malnutrition as a predictor of readmissions in older patients but this has not been verified in a larger population. This study investigated what predictors are associated with early and late readmissions and determined whether nutrition status during index hospitalization can be used as a modifiable predictor of unplanned hospital readmissions.

Design: A retrospective cohort study

Setting: Two tertiary-level hospitals in Australia

Participants: All medical admissions ≥18 years over a period of 1-year

Outcomes: Primary objective was to determine predictors of early (0-7 days) and late (8-180 days) readmissions. Secondary objective was to determine whether nutrition status as determined by malnutrition universal screening tool (MUST) can be used to predict readmissions.

Results: There were 11,750 (44.8%) readmissions within 6-months, with 2,897 (11%) early and 8,853 (33.8%) late readmissions. MUST was completed in 16.2% patients and prevalence of malnutrition during index admission was 31%. Malnourished patients had a higher risk of both early (OR 1.39, 95% CI 1.12-1.73) and late readmissions (1.23, 95% CI 1.06-128). Weekend discharges were less likely to be associated with both early (OR 0.81, 95% CI 0.74-0.91) and late readmissions (OR 0.91, 95% CI 0.84-0.97). Indigenous Australians had a higher risk of early readmissions while those living alone had a higher risk of late readmissions. Patients ≥80 years had a lower risk of early readmissions while admission to intensive care unit (ICU) was associated with a lower risk of late readmissions.

Conclusions: Malnutrition is a strong predictor of unplanned readmissions while weekend discharges are less likely to be associated with readmissions. Targeted nutrition intervention may prevent unplanned hospital readmissions.

Trial registration: ANZCTRN 12617001362381

Strengths and limitations

- A large multicentre study involving 19,924 patients with 26,253 admissions.
- Readmissions to all other hospitals were captured.
- Used Cumulative incidence function (CIF) for unbiased estimation of readmissions over time.
- This study did not take into account psychiatric factors and discharge medications.
- Functional status of the patients at discharge was not determined.

Introduction

Recent advances in medicine have led to a vast improvement in life expectancy but with increasing numbers of patients with multiple clinical problems. Although the length of hospital stay has improved and there has been a decline in the number of beds for acute patients, unplanned hospital readmissions have increased.[1] Hospital readmissions strain the already busy health care settings and not only increase the health care costs but also expose patients to hospitalization associated complications.[2] Medicare data in the US suggests that 20% of patients return to hospital within 30 days of discharge, of which 90% are unplanned admissions with the estimated cost to the extent of US$30 billion.[3] Given a considerable financial burden for hospitals and adverse outcomes for patients, hospital readmissions are increasingly used as quality indicators for institution's performance benchmark with a risk of reduced reimbursements for poorly performing hospitals.[4]

Although numerous readmission prediction tools are available still preventing readmissions has been problematic, as the discriminative power of the available prediction tools has been modest.[5] Zhou et al has highlighted need for rigorous validation of the existing risk-predictive models for potentially avoidable hospital readmissions, as the performance of the existing models is inconsistent.[6] They have suggested that most of the models were developed based on healthcare data from the USA, which might not be applicable to patients from other settings. Furthermore, different factors may influence readmissions over different periods following hospital discharge.[7] Some of these factors are still unidentified and may be potentially modifiable for future targeted interventions.

Very few studies have determined predictors of unplanned readmissions at different periods following hospital discharge in the Australian health care settings. Moreover, the available studies have not captured readmissions to all other hospitals following discharge.[8 9] A recent study has also suggested that malnutrition is a strong predictor of hospital readmissions and mortality but this study included only a small sample of older general medical patients in a single hospital setting.[10] Whether nutrition risk can be used as a predictor of readmissions in a broad range of medical patients needs further confirmation. This study was designed to determine predictors of hospital readmissions in early and late periods following hospital discharge across all medical specialties, in two major teaching hospitals in Australia and captured readmissions to all other hospitals. The other aim was to determine whether admission nutrition status, as determined by the Malnutrition Universal Screening Tool (MUST), can be used to predict hospital readmissions.

Methods

Setting and Study population

This is a retrospective study and data were collected from two large urban teaching hospitals in South Australia. Ethical approval was granted by Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC) no. 216.17 on 4 August 2017 and this study was registered with Australia and New Zealand clinical trials registry (ANZCTRN 12617001362381)**.** This study included all live medical admissions in Flinders Medical Centre (FMC) and Royal Adelaide Hospital (RAH) from 1 January 2016 to 31 December 2016. For this study, a readmission was only counted once as a readmission, relative to the prior index admission. All subsequent admissions then re-entered the cohort as a new index admission. All elective readmissions were excluded from the dataset.

Data sources

In this study, we derived our cohort and variables of interest using the hospital's central computer database. All the data in the two involved health facilities are prospectively collected as part of regular hospital operations.

Objectives

The primary objective for this study was to determine predictors for early readmissions, defined as readmissions within 7 days post discharge from index hospitalization while late readmissions were defined as readmissions within 8-180 days post discharge. The secondary objective was to determine whether nutrition status as determined by the MUST can predict readmissions and can be used as a modifiable risk factor. Only non-elective admissions were included in this study.

Analysis

Variables of interest

Patients were categorized into three groups based upon the pattern of readmission: not readmitted within 180 days (base category), readmitted within 7 days of index admissions (early readmissions) and readmitted within 8 to 180 days after index admission (late readmissions). Patients not readmitted within 180 days were defined as the reference group for subsequent comparisons.

Previous studies have suggested that different variables may be responsible for various stages of readmissions.[11 12] Variables relating to the index admission that may be associated with early readmissions include clinical instability as determined by intensive unit care (ICU) admissions, number of medical emergency response team (MET) calls, complications during admission and length of hospital stay (LOS).[11 13] Late readmissions may be associated with markers of chronic illness burden as reflected by the Charlson comorbidity illness (CCI), social determinants of health including marital status, whether patient was living alone or with family and the socioeconomic status as determined by the composite index of relative socio-economic disadvantage (IRSD).[14 15] IRSD relates to the degree of area based social disadvantage based on low levels of income and education and high levels of unemployment and is provided nationally by the Australian Bureau of Statistics.[16] Nutrition status of the participants during index admission was determined by the use of MUST.[17] It is a requirement that all patients admitted in the RAH and FMC are screened for malnutrition at admission using the MUST. The MUST includes a body mass index (BMI) score, a weight loss score, and an acute disease score and a total MUST score of 0 indicates low risk, 1 medium risk and ≥2 high risk of malnutrition.[18] For this study, patients with a MUST score of 0 were classified as nourished and those with a score ≥1 were classified as malnourished.

Statistical analysis

Data were assessed for normality using skewness and kurtosis (sk) test. Continuous variables are presented as mean (standard deviation; SD) while categorical variables as median (interquartile range; IQR). We used multinomial polytomous logistic regression to model the association between variables of interest and early and late readmissions (with no readmissions within 180 days as the reference). Length of hospital stay (LOS) was adjusted for in hospital mortality. The model was adjusted for following covariates-age, gender and Charlson index and length of hospital stay.

As death is a competing risk for readmissions, the interpretation of Kaplan-Meier survival curve may not be realistic in clinical practice and may overestimate the incidence of readmissions over time.[19] Therefore, we used cumulative incidence functions (CIFs) for unbiased estimation of the probability of readmissions over time according to the nutrition status of the patients determined during the index hospitalization.[20 21] Cumulative risk regression model as suggested by Fine and Gray,[22] determined the subdistribution hazard ratio (SHR) and a CIF curve for readmissions was plotted. The model was adjusted for the following covariates- age, gender, Charlson comorbidity index and length of hospital stay.

All data analyses were performed using STATA 15 (StataCorp College station, Texas, USA) and a p value <0.05 was considered statistically significant.

Results

There were a total of 26,253 admissions, representing 19,924 patients, between 1st January 2016 to 31st December 2016, with 52.3% males. The overall readmission rate at 6-months was 44.8%. A total of 2,897 (11.0% of index admissions) patients were readmitted within 7 days of discharge (early readmissions) whereas 8, 853 (33.8% of index admissions) were readmitted within 8-180 days of discharge (late readmissions)(Table 1). The distribution of readmissions by post-discharge day is shown in Figure 1, with 24.7% of readmissions occurring in the early period, and 75.3% occurring late after hospital discharge. MUST was completed in 4251 (16.2%) of patients during index admission and prevalence of malnutrition according to the MUST was 31%. Majority of patients (80.5%) were discharged over the weekdays and only 19.5% discharges occurred over the weekends.

Table 1 Initial hospitalization and patient characteristics by readmission status

Variable	**Early Readmissions (0-7 days) (n = 2897, 11.0%)**	**Late Readmissions (8-180 days) (n = 8853, 33.8%)**	**No Readmission (within 180 days) (n = 14503, 55.2%)**
Age n (%)			
<40	305 (10.5)	863 (9.8)	1616 (11.1)
41- 59	664 (22.9)	1869 (21.1)	3156 (21.8)
60 - 79	1189 (41.0)	3525 (39.8)	5343 (36.8)
>80	739 (25.5)	2596 (29.3)	4388 (30.3)
Sex Male n (%)	1588 (54.8)	4688 (53.0)	7528 (52.0)
Confirmed Indigenous status n (%)	169 (5.8)	249 (2.8)	329 (2.3)
Marital status n (%)			
Single	96 (7.9)	398 (9.2)	496 (7.3)
Married/Partnered	532 (43.7)	1957 (45.2)	2962 (43.4)
Divorced/Separated	138 (11.4)	513 (11.8)	496 (7.3)
Home alone n (%)	387 (31.9)	1369 (31.6)	1957 (28.6)
LOS median (IQR)	4.0 (6.1)	3.7 (5.0)	2.8 (4.0)
ICU hours mean (SD)	5.9 (37.2)	3.3 (22.1)	3.5 (33.4)
MET call during admission n (%)	91 (7.5)	274 (6.3)	475 (6.9)
Complications during admission n (%)	707 (24.4)	1745 (19.7)	2725 (18.8)
Previous health care use median (IQR)	1.0 (2.0)	1.0 (2.0)	0 (1.0)
Malnourished n (%)	172 (38.0)	514 (33.2)	632 (28.1)
MUST score[a] mean (SD)	0.38 (0.48)	0.33 (0.47)	0.27 (0.44)

BMI mean (SD)	26.5 (7.3)	26.6 (7.6)	27.0 (7.4)
Weekend discharge	487 (16.8)	1645 (18.6)	2578 (19.5)
Discharge time n (%)			
0600-1200	817 (28.2)	2453 (27.7)	4031 (27.8)
1201-1800	1854 (64.0)	5811 (65.6)	8843 (61.0)
1801-0559	226 (7.8)	589 (6.7)	1629 (11.2)
Charlson index mean (SD)	2.3 (2.3)	2.0 (2.3)	1.4 (2.0)
IRSD[b] score mean (SD)	5.1 (2.8)	5.3 (2.7)	5.4 (2.9)

[a]Higher MUST score indicates worse nutrition status
[b]Higher IRSD score indicates better socioeconomic status
LOS, length of hospital stay; IQR, interquartile range; ICU, intensive care unit SD, standard deviation; MET, medical emergency response team; MUST, malnutrition universal screening tool; BMI, body mass index; IRSD, index of relative socioeconomic disadvantage

Predictors of early and late readmissions

After adjusted analyses, this study found that higher Charlson index, the number of admissions in the prior 6 months, LOS of index admission and MET calls were associated with higher risk of both early and later readmissions. Similarly, patients who were single, divorced or separated and socially disadvantaged had higher odds of a readmission in both periods (Table 2).

Patients who were malnourished had a 39% higher risk of early readmission (OR 1.39, 95% CI 1.12-1.73) and this risk remained elevated at 23% in later period following discharge (OR 1.23, 95% CI 1.06-1.42). The adjusted subdistribution hazard ratio for readmissions with mortality as a competing risk was 1.17 (95% CI 1.06-1.28) and the CIF curve is shown in Figure 2.

Patients who were discharged over the weekends had a lower odds of being admitted in both early 0.81, 95% 0.74-0.91) and late periods (0.91, 95% 0.84-0.97) following discharge compared to those discharged over the weekdays (Table 2). Patients who were discharged over the weekend were found to have a shorter LOS (median 2.3

(IQR 1.2-4.1) vs. 3.6 (IQR 1.8-6.8, p<0.001), fewer nosocomial complications (12.9% vs. 19.3%, p<0.001), were less likely to be admitted in the ICU (3.3% vs. 4.9%, p<0.001) during index hospitalization and were more likely to be discharged home rather than a residential facility (96.1% vs. 91.2%, p<0.001) as compared to those discharged over the weekdays.

Predictors of early readmissions

Indigenous patients were more likely to be readmitted early after hospital discharge (OR 2.00, 95% CI 1.64-2.45) but early readmissions were less likely among patients who were ≥80 years of age (OR 0.81, 95% CI 0.70-0.94) (Table 2).

Predictors of late readmissions

Late readmissions occurred more likely among patients who were living alone at home (OR 1.20, 95% CI 1.08-1.33) but were less often if patient had been admitted to the ICU during index admission (OR 0.70, 95% CI 0.59-0.84) (Table 2).

Table 2 Multivariable model for early and late readmissions

Variable	Early Readmissions (0-7 days) Odds ratio (95% CI)[a]	Late Readmissions (8-180 days) Odds ratio (95% CI)
Age		
≤40 (reference)	-	-
41-59	0.90 (0.77-1.05)	0.98 (0.89-1.09)
60-79	0.93 (0.80-1.07)	1.09 (0.99-1.20)
≥80	0.81 (0.70-0.94)	1.01 (0.88-1.70)
Male gender	1.07 (0.99-1.16)	1.02 (0.96-1.08)
Indigenous status		
Non-indigenous (reference)	-	-
Indigenous	2.00 (1.64-2.45)	1.06 (0.89-1.26)
Marital status		
Married (reference)	-	-
Single	1.34 (1.04-1.73)	1.40 (1.19-1.63)
Divorced/Separated	1.50 (1.20-1.86)	1.54 (1.33-1.78)

Home status		
Lives with family (reference)	-	-
Lives alone	1.13 (0.96-1.33)	1.20 (1.08-1.33)
Charlson comorbidity index	1.27 (1.24-1.29)	1.18 (1.16-1.20)
Length of stay (index admission, in days)	1.02 (1.02-1.03)	1.01 (1.01-1.02)
Admissions in last 6 months (per admission)	3.20 (2.95-3.50)	2.93 (2.77-3.10)
Socio-economic status[a]		
Least disadvantaged (reference)	-	-
Most disadvantaged	1.40 (1.22-1.60)	1.20 (1.10-1.31)
Day of discharge		
Weekday (reference)	-	-
Weekend	0.81 (0.74-0.91)	0.91 (0.84-0.97)
Time of discharge		
AM (0600-1159)	0.99 (0.90-1.09)	0.96 (0.89-1.02)
Reference (1200-1759)	-	-
PM (1801-0559)	1.11 (0.95-1.25)	0.87 (0.76-1.00)
ICU stay during admission	1.03 (0.86-1.07)	0.70 (0.59-0.84)
MET calls during admission	1.30 (1.01-1.70)	1.27 (1.01-1.17)
Complications during admission	1.29 (1.16-1.43)	1.09 (1.11-1.34)
BMI during index admission	0.99 (0.98-1.01)	0.98 (0.97-1.01)
MUST class		
Nourished (reference)	-	-
Malnourished	1.39 (1.12-1.73)	1.23 (1.06-1.42)

[a]Odds ratios were derived using a multinomial logistic regression, using readmission category (none within 180 days, early (within 7 days) and late (8-180 days) readmissions as the outcome variable
[b]Socioeconomic status was determined by index of relative socio-economic disadvantage (IRSD)
CI, confidence interval; ICU, intensive care unit; MET; medical emergency response team; BMI, body mass index; MUST, malnutrition universal screening tool

Discussion

The results of the present study highlight predictors of readmissions in early and late periods following hospital discharge in the Australian healthcare settings. In line with the previous studies,[3 5 13] we found that higher number of comorbidities, LOS and higher complications during hospital admission were associated with a higher readmission risk. A significant finding of this study is that nutrition status during index admission, predicts both early and late readmissions. Patients who were malnourished during index hospitalization had a 39% higher risk of being readmitted early after hospital discharge and this risk remains significantly increased even in the later periods following hospital discharge. Our study validates the findings of a previous study[10] that impaired nutrition status during index hospitalization increases the risk of readmissions among medical patients across all specialties. The prevalence of malnutrition in our study was 31%, which is comparable to other studies among hospitalized patients.[23] The concerning finding is that only 16% of the patients underwent nutrition screening during hospital admission, which highlights that a significant proportion of malnourished patients are missed. Studies indicate that early nutrition intervention may have a beneficial effect in improving nutritional and clinical outcomes among malnourished patients.[24 25] Stratton et al in their meta-analysis involving 1190 patients, found that readmissions rate was significantly reduced in patients who received oral nutrition supplements (ONS) (33.8% vs. 23.9%, $p<0.001$).[25] However, the studies involved in this meta-analysis included only older patients and whether nutrition supplementation can reduce readmissions in younger patients is still unknown. There is a window of opportunity to target malnutrition among hospitalized patients and future intervention studies should target patients of all age groups to see if it helps reduce readmissions.

We also found that patients who were discharged on weekends had lower readmission rates (both in early and late periods following discharge) as compared to those discharged over the weekdays. One explanation could be that patients who were considered at a high risk for readmission may already have been selected for weekday discharge. In addition, this study found that patients discharged on a weekend had a shorter length of hospital stay, suffered fewer complications during admission and were more likely to be discharged home, suggesting that these patients may have been less medically complicated. These findings suggest that hospitals need not worry that weekend discharges will adversely affect their readmission statistics, however, the results need to be interpreted with caution as patients discharged on weekends were healthier and less likely to be malnourished. It is also possible that these patients had fewer post-hospital needs than those discharged over the weekdays. Our study results are in line with a similar study conducted by Cloyd et al who found lower 30-day readmission rates in patients discharged over the weekends but this study included only surgical patients.[26]

We found that indigenous status is a strong predictor of early readmissions but not late readmissions among Australian hospitalized patients. Indigenous Australians are socially isolated and are among the most disadvantaged groups in Australia.[27] There is a very high incidence of self-discharge or discharge against medical advice among indigenous Australians and it is possible that non-resolution of acute illness may be a contributing factor for early readmissions in this group.[28] We also found that readmissions were less frequent among very old people. The LOS among patients older than 80 years was significantly longer in our patients (which could indicate delayed discharge) and they were more likely to be discharged to a NH rather home, which could be the reason for their less frequent presentation early after hospital discharge.

With regards to late readmissions, we found that patients living alone are more likely to be readmitted than those living with family, this finding is in line with previous studies[29 30] but unlike other studies[11 31] we found that patients who had an ICU admission are less likely to have late readmissions. As ICU admission is a marker of clinical instability,[32] it is more likely to be associated with an early rather than late readmission. It is also possible that these patients had a higher mortality after hospital discharge, which could have been a competing risk for readmissions, and thus had fewer late readmissions.

In conclusion, multiple factors including admission nutrition status predict rehospitalization. Moreover, this study adds significant evidence that weekend discharges are not associated with an increased risk of readmissions in medical patients.

Limitations

The results of this study should be interpreted in the context of the data analyzed. Our preference to compare readmissions within first week to admissions within 8-180 days following discharge, were based on clinical judgment and analysis using an alternate time period (i.e., 14 days vs. 30 days vs. 90 days) might reveal different results. This study did not consider other important factors such as functional status and psychiatric illnesses, which can have a significant impact on unplanned readmissions. We did not have information about the discharge medications, which have been shown to be of critical importance and may lead to adverse events after discharge[33]. Lastly, although this was a large sample, data from only two hospitals was included, which could limit generalizability. Strengths include large sample size and inclusion of all readmissions to all hospitals in the state.

Conclusion

Among patients discharged from hospital, malnutrition as determined by the MUST is a risk factor for both early and late readmissions There is some indication that early readmissions may have different causal pathways than late readmissions with weekend discharges associated with a significantly lower risk of readmissions.

Contributors: YS and CT designed the study and YS, CT, PH and CH carried out the analysis and interpretation. YS and CT lead the study and CH was responsible for data acquisition. YS, PH and CH provided statistical input. YS wrote the manuscript, which was critically reviewed by CT. CT, BK, RS and MM edited the manuscript. All authors approved final manuscript.

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Figure 1 Distribution of readmissions

Figure 2 Cumulative incidence estimate model for readmissions with death as a competing risk. Competing risk regression was used to estimate subdistribution hazard ratio (SHR), 1.17 (95% CI 1.06-1.28). Model adjusted for covariates-age, sex, charlson index and length of hospital stay.

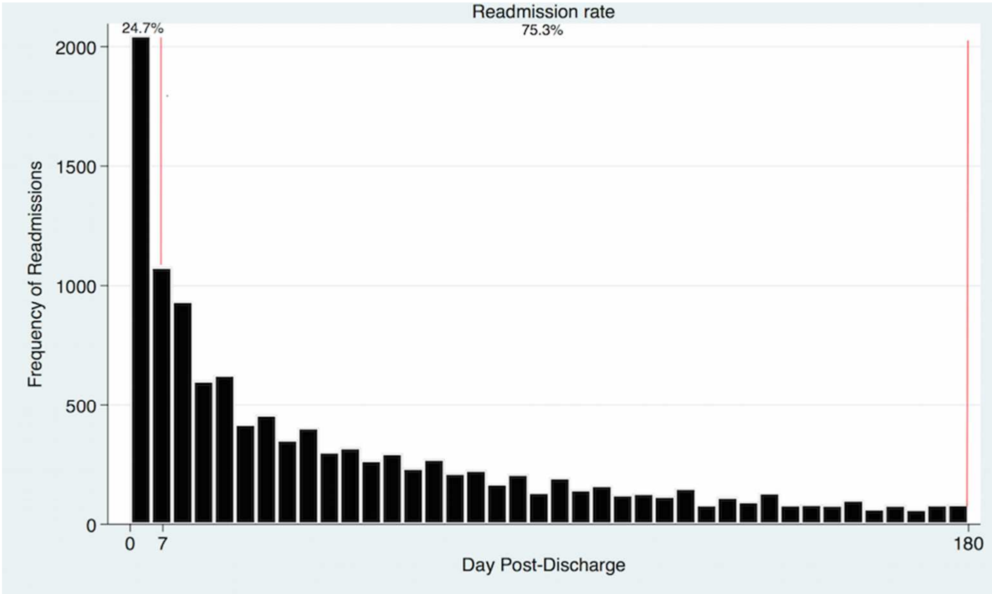

Figure 1 Distribution of readmissions

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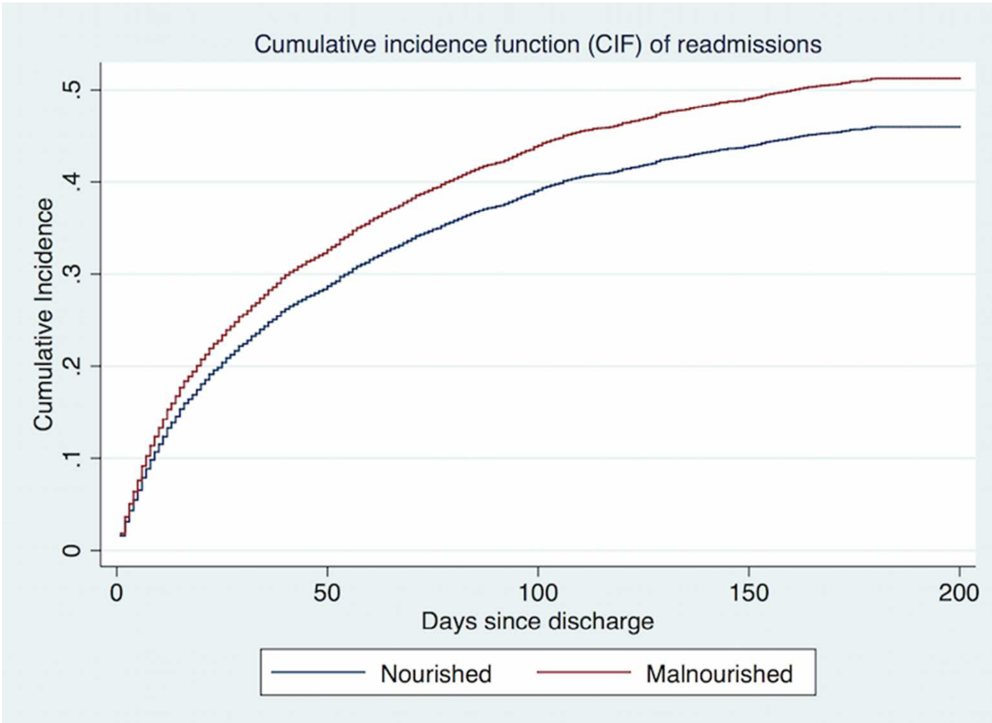

Figure 2 Cumulative incidence estimate model for readmissions with death as a competing risk. Competing risk regression was used to estimate subdistribution hazard ratio (SHR), 1.17 (95% CI 1.06-1.28). Model adjusted for covariates-age, sex, charlson index and length of hospital stay.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page 1 and page 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7
Methods			
Study design	4	Present key elements of study design early in the paper	Pages 7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pages 7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 8-9
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pages 10-11, Table 1
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A information in Table 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pages 10-11 and Tables 1-2
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	Pages 12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 11-13, Table 2
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pages 14-15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Factors influencing early and late readmissions in Australian hospitalised patients and investigating role of admission nutrition status as a predictor of hospital readmissions: a cohort study

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Factors influencing early and late readmissions in Australian hospitalised patients and investigating role of admission nutrition status as a predictor of hospital readmissions: a cohort study

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Abstract

Objectives: Limited studies have identified predictors of early and late hospital readmissions in Australian healthcare settings. Some of these predictors may be modifiable through targeted interventions. A recent study has identified malnutrition as a predictor of readmissions in older patients but this has not been verified in a larger population. This study investigated what predictors are associated with early and late readmissions and determined whether nutrition status during index hospitalization can be used as a modifiable predictor of unplanned hospital readmissions.

Design: A retrospective cohort study

Setting: Two tertiary-level hospitals in Australia

Participants: All medical admissions ≥18 years over a period of 1-year

Outcomes: Primary objective was to determine predictors of early (0-7 days) and late (8-180 days) readmissions. Secondary objective was to determine whether nutrition status as determined by malnutrition universal screening tool (MUST) can be used to predict readmissions.

Results: There were 11,750 (44.8%) readmissions within 6-months, with 2,897 (11%) early and 8,853 (33.8%) late readmissions. MUST was completed in 16.2% patients and prevalence of malnutrition during index admission was 31%. Malnourished patients had a higher risk of both early (OR 1.39, 95% CI 1.12-1.73) and late readmissions (1.23, 95% CI 1.06-128). Weekend discharges were less likely to be associated with both early (OR 0.81, 95% CI 0.74-0.91) and late readmissions (OR 0.91, 95% CI 0.84-0.97). Indigenous Australians had a higher risk of early readmissions while those living alone had a higher risk of late readmissions. Patients ≥80 years had a lower risk of early readmissions while admission to intensive care unit (ICU) was associated with a lower risk of late readmissions.

Conclusions: Malnutrition is a strong predictor of unplanned readmissions while weekend discharges are less likely to be associated with readmissions. Targeted nutrition intervention may prevent unplanned hospital readmissions.

Trial registration: ANZCTRN 12617001362381

Strengths and limitations

- A large multicentre study involving 19,924 patients with 26,253 admissions.
- Readmissions to all other hospitals were captured.
- Used Cumulative incidence function (CIF) for unbiased estimation of readmissions over time.
- This study did not take into account psychiatric factors and discharge medications.
- Functional status of the patients at discharge was not determined.

Introduction

Recent advances in medicine have led to a vast improvement in life expectancy but with increasing numbers of patients with multiple clinical problems. Although the length of hospital stay has improved and there has been a decline in the number of beds for acute patients, unplanned hospital readmissions have increased.[1] Hospital readmissions strain the already busy health care settings and not only increase the health care costs but also expose patients to hospitalization associated complications.[2] Medicare data in the US suggests that 20% of patients return to hospital within 30 days of discharge, of which 90% are unplanned admissions with the estimated cost to the extent of US$30 billion.[3] Given a considerable financial burden for hospitals and adverse outcomes for patients, hospital readmissions are increasingly used as quality indicators for institution's performance benchmark with a risk of reduced reimbursements for poorly performing hospitals.[4]

Although numerous readmission prediction tools are available still preventing readmissions has been problematic, as the discriminative power of the available prediction tools has been modest.[5] Zhou et al has highlighted need for rigorous validation of the existing risk-predictive models for potentially avoidable hospital readmissions, as the performance of the existing models is inconsistent.[6] They have suggested that most of the models were developed based on healthcare data from the USA, which might not be applicable to patients from other settings. Furthermore, different factors may influence readmissions over different periods following hospital discharge.[7] Studies have identified that some of the factors responsible for readmissions e.g. medication errors, may be potentially modifiable and there may be similar other factors which are yet to be identified and could be the target for future interventions.[8]

Very few studies have determined predictors of unplanned readmissions at different periods following hospital discharge in the Australian health care settings. Moreover, the available studies have not captured readmissions to all other hospitals following discharge.[9 10] Malnutrition is associated with adverse health outcomes for patients and leads to increased health care costs.[11 12] A recent study has suggested that malnutrition is a strong predictor of hospital readmissions and mortality but this study included only a small sample of older general medical patients in a single hospital setting.[13] Whether nutrition risk can be used as a predictor of readmissions in a broad range of medical patients needs further confirmation. This study was designed to determine predictors of hospital readmissions in early and late periods following hospital discharge across all medical specialties, in two major teaching hospitals in Australia and captured readmissions to all other hospitals. The other aim was to determine whether admission nutrition status, as determined by the Malnutrition Universal Screening Tool (MUST), can be used to predict hospital readmissions.

Methods

Setting and Study population

This is a retrospective study and data were collected from two large urban teaching hospitals in South Australia. Ethical approval was granted by Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC) no. 216.17 on 4 August

2017 and this study was registered with Australia and New Zealand clinical trials registry (ANZCTRN 12617001362381)**.** This study included all live medical admissions in Flinders Medical Centre (FMC) and Royal Adelaide Hospital (RAH) from 1 January 2016 to 31 December 2016. For this study, a readmission was only counted once as a readmission, relative to the prior index admission. All subsequent admissions then re-entered the cohort as a new index admission. All elective readmissions were excluded from the dataset.

Data sources

In this study, we derived our cohort and variables of interest using the hospital's central computer database. All the data in the two involved health facilities are prospectively collected as part of regular hospital operations.

Objectives

The primary objective for this study was to determine predictors for early readmissions, defined as readmissions within 7 days post discharge from index hospitalization while late readmissions were defined as readmissions within 8-180 days post discharge. The secondary objective was to determine whether nutrition status as determined by the MUST can predict readmissions and can be used as a modifiable risk factor. Only non-elective admissions were included in this study.

Analysis

Variables of interest

Patients were categorized into three groups based upon the pattern of readmission: not readmitted within 180 days (base category), readmitted within 7 days of index admissions (early readmissions) and readmitted within 8 to 180 days after index admission (late readmissions). Patients not readmitted within 180 days were defined as the reference group for subsequent comparisons.

Previous studies have suggested that different variables may be responsible for various stages of readmissions.[14 15] Variables relating to the index admission that may be associated with early readmissions include clinical instability as determined by intensive unit care (ICU) admissions, number of medical emergency response team (MET) calls, complications during admission and length of hospital stay (LOS).[14 16] Late readmissions may be associated with markers of chronic illness burden as reflected by the Charlson comorbidity illness (CCI), social determinants of health including marital status, whether patient was living alone or with family and the socioeconomic status as determined by the composite index of relative socio-economic disadvantage (IRSD).[17 18] IRSD relates to the degree of area based social disadvantage based on low levels of income and education and high levels of unemployment and is provided nationally by the Australian Bureau of Statistics.[19] Nutrition status of the participants during index admission was determined by the use of MUST.[20] It is a requirement that all patients admitted in the RAH and FMC are screened for malnutrition at admission using the MUST. The MUST includes a body mass index (BMI) score, a weight loss score, and an acute disease score and a total MUST score of 0 indicates low risk, 1 medium risk and ≥2 high risk of malnutrition.[21]

For this study, patients with a MUST score of 0 were classified as nourished and those with a score ≥1 were classified as malnourished.

Statistical analysis

Data were assessed for normality using skewness and kurtosis (sk) test. Continuous variables are presented as mean (standard deviation; SD) while categorical variables as median (interquartile range; IQR). We used multinomial polytomous logistic regression to model the association between variables of interest and early and late readmissions (with no readmissions within 180 days as the reference). LOS was adjusted for in hospital mortality. The model was adjusted for following covariates- age, gender and CC1 and LOS.

As death is a competing risk for readmissions, the interpretation of Kaplan-Meier survival curve may not be realistic in clinical practice and may overestimate the incidence of readmissions over time.[22] Therefore, we used cumulative incidence functions (CIFs) for unbiased estimation of the probability of readmissions over time according to the nutrition status of the patients determined during the index hospitalization.[23 24] Cumulative risk regression model as suggested by Fine and Gray,[25] determined the subdistribution hazard ratio (SHR) and a CIF curve for readmissions was plotted. The model was adjusted for the following covariates- age, gender, CCI and LOS.

All data analyses were performed using STATA 15 (StataCorp College station, Texas, USA) and a p value <0.05 was considered statistically significant.

Patient and public involvement

There was no patient or public involvement as this study involved only retrospective data collection.

Results

There were a total of 26,253 admissions, representing 19,924 patients, between 1st January 2016 to 31st December 2016, with 52.3% males. The overall readmission rate at 6-months was 44.8%. A total of 2,897 (11.0% of index admissions) patients were readmitted within 7 days of discharge (early readmissions) whereas 8, 853 (33.8% of index admissions) were readmitted within 8-180 days of discharge (late readmissions)(Table 1). The distribution of readmissions by post-discharge day is shown in Figure 1, with 24.7% of readmissions occurring in the early period, and 75.3% occurring late after hospital discharge. MUST was completed in 4251 (16.2%) of patients during index admission and prevalence of malnutrition according to the MUST was 31%. Patients who underwent MUST screening were significantly older (67.8 years (SD 18.4) vs. 66.0 years (SD 18.7), P<0.001), had a higher CCI (1.8 (SD 2.3) vs. 1.7 (SD 2.2), P<0.005) and a longer LOS (5.7 days (IQR 8.7) vs. 3.1 days (IQR 4.5), P<0.001) but were less likely to be of indigenous status (84 (1.8%) vs. 670 (2.8%), P <0.001) than those who missed MUST screening. Majority of patients (80.5%) were discharged over the weekdays and only 19.5% discharges occurred over the weekends.

Table 1 Initial hospitalization and patient characteristics by readmission status

Variable	**Early Readmissions (0-7 days) (n = 2897, 11.0%)**	**Late Readmissions (8-180 days) (n = 8853, 33.8%)**	**No Readmission (within 180 days) (n = 14503, 55.2%)**

Age n (%)			
<40	305 (10.5)	863 (9.8)	1616 (11.1)
41- 59	664 (22.9)	1869 (21.1)	3156 (21.8)
60 - 79	1189 (41.0)	3525 (39.8)	5343 (36.8)
>80	739 (25.5)	2596 (29.3)	4388 (30.3)
Sex Male n (%)	1588 (54.8)	4688 (53.0)	7528 (52.0)
Confirmed Indigenous status n (%)	169 (5.8)	249 (2.8)	329 (2.3)
Marital status n (%)			
Single	96 (7.9)	398 (9.2)	496 (7.3)
Married/Partnered	532 (43.7)	1957 (45.2)	2962 (43.4)
Divorced/Separated	138 (11.4)	513 (11.8)	496 (7.3)
Home alone n (%)	387 (31.9)	1369 (31.6)	1957 (28.6)
LOS median (IQR)	4.0 (6.1)	3.7 (5.0)	2.8 (4.0)
ICU hours mean (SD)	5.9 (37.2)	3.3 (22.1)	3.5 (33.4)
MET call during admission n (%)	91 (7.5)	274 (6.3)	475 (6.9)
Complications during admission n (%)	707 (24.4)	1745 (19.7)	2725 (18.8)
Previous health care use median (IQR)	1.0 (2.0)	1.0 (2.0)	0 (1.0)
Malnourished n (%)	172 (37.6)	514 (33.2)	632 (28.1)
MUST score[a] mean (SD)	0.38 (0.48)	0.33 (0.47)	0.27 (0.44)
MUST group[b] n (%)			
Low risk	286 (62.4)	1033 (66.8)	1614 (71.9)
Medium risk	65 (14.2)	205 (13.2)	252 (11.2)
High risk	107 (23.4)	309 (20.0)	380 (16.9)
BMI mean (SD)	26.5 (7.3)	26.6 (7.6)	27.0 (7.4)
Weekend discharge	487 (16.8)	1645 (18.6)	2578 (19.5)
Discharge time n (%)			
0600-1200	817 (28.2)	2453 (27.7)	4031 (27.8)
1201-1800	1854 (64.0)	5811 (65.6)	8843 (61.0)
1801-0559	226 (7.8)	589 (6.7)	1629 (11.2)
Charlson index mean (SD)	2.3 (2.3)	2.0 (2.3)	1.4 (2.0)
IRSD[c] score mean (SD)	5.1 (2.8)	5.3 (2.7)	5.4 (2.9)

[a]Higher MUST score indicates worse nutrition status
[b]MUST group, Low risk = MUST score 0, Medium risk = MUST score 1, High risk = MUST score ≥2
[c]Higher IRSD score indicates better socioeconomic status
LOS, length of hospital stay; IQR, interquartile range; ICU, intensive care unit SD, standard deviation; MET, medical emergency response team; MUST, malnutrition universal screening tool; BMI, body mass index; IRSD, index of relative socioeconomic disadvantage

Predictors of early and late readmissions

After adjusted analyses, this study found that higher Charlson index, the number of admissions in the prior 6 months, LOS of index admission and MET calls were associated with higher risk of both early and later readmissions. Similarly, patients who were single, divorced or separated and socially disadvantaged had higher odds of a readmission in both periods (Table 2).

Patients who were malnourished had a 39% higher risk of early readmission (OR 1.39, 95% CI 1.12-1.73) and this risk remained elevated at 23% in later period following discharge (OR 1.23, 95% CI 1.06-1.42). The adjusted subdistribution hazard ratio for readmissions with mortality as a competing risk was 1.17 (95% CI 1.06-1.28) and the CIF curve is shown in Figure 2.

Patients who were discharged over the weekends had a lower odds of being admitted in both early 0.81, 95% 0.74-0.91) and late periods (0.91, 95% 0.84-0.97) following discharge compared to those discharged over the weekdays (Table 2). Patients who were discharged over the weekend were found to have a shorter LOS (median 2.3 (IQR 1.2-4.1) vs. 3.6 (IQR 1.8-6.8, p<0.001), fewer nosocomial complications (12.9% vs. 19.3%, p<0.001), were less likely to be admitted in the ICU (3.3% vs. 4.9%, p<0.001) during index hospitalization and were more likely to be discharged home rather than a residential facility (96.1% vs. 91.2%, p<0.001) as compared to those discharged over the weekdays.

Predictors of early readmissions

Indigenous patients were more likely to be readmitted early after hospital discharge (OR 2.00, 95% CI 1.64-2.45) but early readmissions were less likely among patients who were ≥80 years of age (OR 0.81, 95% CI 0.70-0.94) (Table 2).

Predictors of late readmissions

Late readmissions occurred more likely among patients who were living alone at home (OR 1.20, 95% CI 1.08-1.33) but were less often if patient had been admitted to the ICU during index admission (OR 0.70, 95% CI 0.59-0.84) (Table 2).

Table 2 Multivariable model for early and late readmissions

Variable	Early Readmissions (0-7 days) Odds ratio (95% CI)[a]	Late Readmissions (8-180 days) Odds ratio (95% CI)
Age		
≤40 (reference)	-	-
41-59	0.90 (0.77-1.05)	0.98 (0.89-1.09)
60-79	0.93 (0.80-1.07)	1.09 (0.99-1.20)
≥80	0.81 (0.70-0.94)	1.01 (0.88-1.70)
Male gender	1.07 (0.99-1.16)	1.02 (0.96-1.08)
Indigenous status		
Non-indigenous (reference)	-	-
Indigenous	2.00 (1.64-2.45)	1.06 (0.89-1.26)
Marital status		
Married (reference)	-	-
Single	1.34 (1.04-1.73)	1.40 (1.19-1.63)
Divorced/Separated	1.50 (1.20-1.86)	1.54 (1.33-1.78)
Home status		
Lives with family (reference)	-	-
Lives alone	1.13 (0.96-1.33)	1.20 (1.08-1.33)
Charlson comorbidity	1.27 (1.24-1.29)	1.18 (1.16-1.20)

index		
Length of stay (index admission, in days)	1.02 (1.02-1.03)	1.01 (1.01-1.02)
Admissions in last 6 months (per admission)	3.20 (2.95-3.50)	2.93 (2.77-3.10)
Socio-economic status[a]		
Least disadvantaged (reference)	-	-
Most disadvantaged	1.40 (1.22-1.60)	1.20 (1.10-1.31)
Day of discharge		
Weekday (reference)	-	-
Weekend	0.81 (0.74-0.91)	0.91 (0.84-0.97)
Time of discharge		
AM (0600-1159)	0.99 (0.90-1.09)	0.96 (0.89-1.02)
Reference (1200-1759)	-	-
PM (1801-0559)	1.11 (0.95-1.25)	0.87 (0.76-1.00)
ICU stay during admission	1.03 (0.86-1.07)	0.70 (0.59-0.84)
MET calls during admission	1.30 (1.01-1.70)	1.27 (1.01-1.17)
Complications during admission	1.29 (1.16-1.43)	1.09 (1.11-1.34)
BMI during index admission	0.99 (0.98-1.01)	0.98 (0.97-1.01)
MUST class		
Nourished (reference)	-	-
Malnourished	1.39 (1.12-1.73)	1.23 (1.06-1.42)

[a]Odds ratios were derived using a multinomial logistic regression, using readmission category (none within 180 days, early (within 7 days) and late (8-180 days) readmissions as the outcome variable

[b]Socioeconomic status was determined by index of relative socio-economic disadvantage (IRSD)

CI, confidence interval; ICU, intensive care unit; MET; medical emergency response team; BMI, body mass index; MUST, malnutrition universal screening tool

Discussion

The results of the present study highlight predictors of readmissions in early and late periods following hospital discharge in the Australian healthcare settings. In line with the previous studies,[3 5 16] we found that higher number of comorbidities, LOS and higher complications during hospital admission were associated with a higher readmission risk. A significant finding of this study is that nutrition status during index admission, predicts both early and late readmissions. Patients who were malnourished during index hospitalization had a 39% higher risk of being readmitted early after hospital discharge and this risk remains significantly increased even in the later periods following hospital discharge. Our study validates the findings of a previous study[13] that impaired nutrition status during index hospitalization increases the risk of readmissions among medical patients across all specialties. The prevalence of malnutrition in our study was 31%, which is comparable to other studies among hospitalized patients.[26] The concerning finding is that only 16% of the patients underwent nutrition screening during hospital admission, which highlights that a significant proportion of malnourished patients are missed. Studies indicate that early nutrition intervention may have a beneficial effect in improving nutritional and clinical outcomes among malnourished patients.[27 28] Stratton et al in their meta-analysis involving 1190 patients, found that readmissions rate was significantly reduced in patients who received oral nutrition supplements (ONS) (33.8% vs. 23.9%, p<0.001).[28] However, the studies involved in this meta-analysis included only older patients and whether nutrition supplementation can reduce readmissions in younger patients is still unknown. There is a window of opportunity to target malnutrition among hospitalized patients and future intervention studies should target patients of all age groups to see if it helps reduce readmissions.

We also found that patients who were discharged on weekends had lower readmission rates (both in early and late periods following discharge) as compared to those discharged over the weekdays. One explanation could be that patients who were considered at a high risk for readmission may already have been selected for weekday discharge. In addition, this study found that patients discharged on a weekend had a shorter length of hospital stay, suffered fewer complications during admission and were more likely to be discharged home, suggesting that these patients may have been less medically complicated. These findings suggest that hospitals need not worry that weekend discharges will adversely affect their readmission statistics, however, the results need to be interpreted with caution as patients discharged on weekends were healthier and less likely to be malnourished. It is also possible that these patients had fewer post-hospital needs than those discharged over the weekdays. Our study results are in line with a similar study conducted by Cloyd et al who found lower 30-day readmission rates in patients discharged over the weekends but this study included only surgical patients.[29]

We found that indigenous status is a strong predictor of early readmissions but not late readmissions among Australian hospitalized patients. Indigenous Australians are socially isolated and are among the most disadvantaged groups in Australia.[30] There is a very high incidence of self-discharge or discharge against medical advice among indigenous Australians and it is possible that non-resolution of acute illness may be a contributing factor for early readmissions in this group.[31] We also found that readmissions were less frequent among very old people. The LOS among patients older than 80 years was significantly longer in our patients (which could indicate delayed discharge) and they were more likely to be discharged to a NH rather home, which could be the reason for their less frequent presentation early after hospital discharge.

With regards to late readmissions, we found that patients living alone are more likely to be readmitted than those living with family, this finding is in line with previous studies[32 33] but unlike other studies[14 34] we found that patients who had an ICU admission are less likely to have late readmissions. As ICU admission is a marker of clinical instability,[35] it is more likely to be associated with an early rather than late readmission. It is also possible that these patients had a higher mortality after hospital discharge, which could have been a competing risk for readmissions, and thus had fewer late readmissions.

In conclusion, multiple factors including admission nutrition status predict rehospitalization. Moreover, this study adds significant evidence that weekend discharges are not associated with an increased risk of readmissions in medical patients.

Limitations

The results of this study should be interpreted in the context of the data analyzed. Our preference to compare readmissions within first week to admissions within 8-180 days following discharge, were based on clinical judgment and analysis using an alternate time period (i.e., 14 days vs. 30 days vs. 90 days) might reveal different results. This study did not consider other important factors such as functional status and psychiatric illnesses, which can have a significant impact on unplanned readmissions. We did not have information about the discharge medications, which have been shown to be of critical importance and may lead to adverse events after discharge[8]. Lastly, although this was a large sample, data from only two hospitals was included, which could limit generalizability. Strengths include large sample size and inclusion of all readmissions to all hospitals in the state.

Conclusion

Among patients discharged from hospital, malnutrition as determined by the MUST is a risk factor for both early and late readmissions There is some indication that early readmissions may have different causal pathways than late readmissions with weekend discharges associated with a significantly lower risk of readmissions.

Contributors: YS and CT designed the study and YS, CT, PH and CH carried out the analysis and interpretation. YS and CT lead the study and CH was responsible for data acquisition. YS, PH and CH provided statistical input. YS wrote the manuscript, which was critically reviewed by CT. CT, BK, RS and MM edited the manuscript. All authors approved final manuscript.

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Competing interests: None

Data sharing statement: The data that support the findings of this study are available from the corresponding author upon reasonable request and only after permission by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC).

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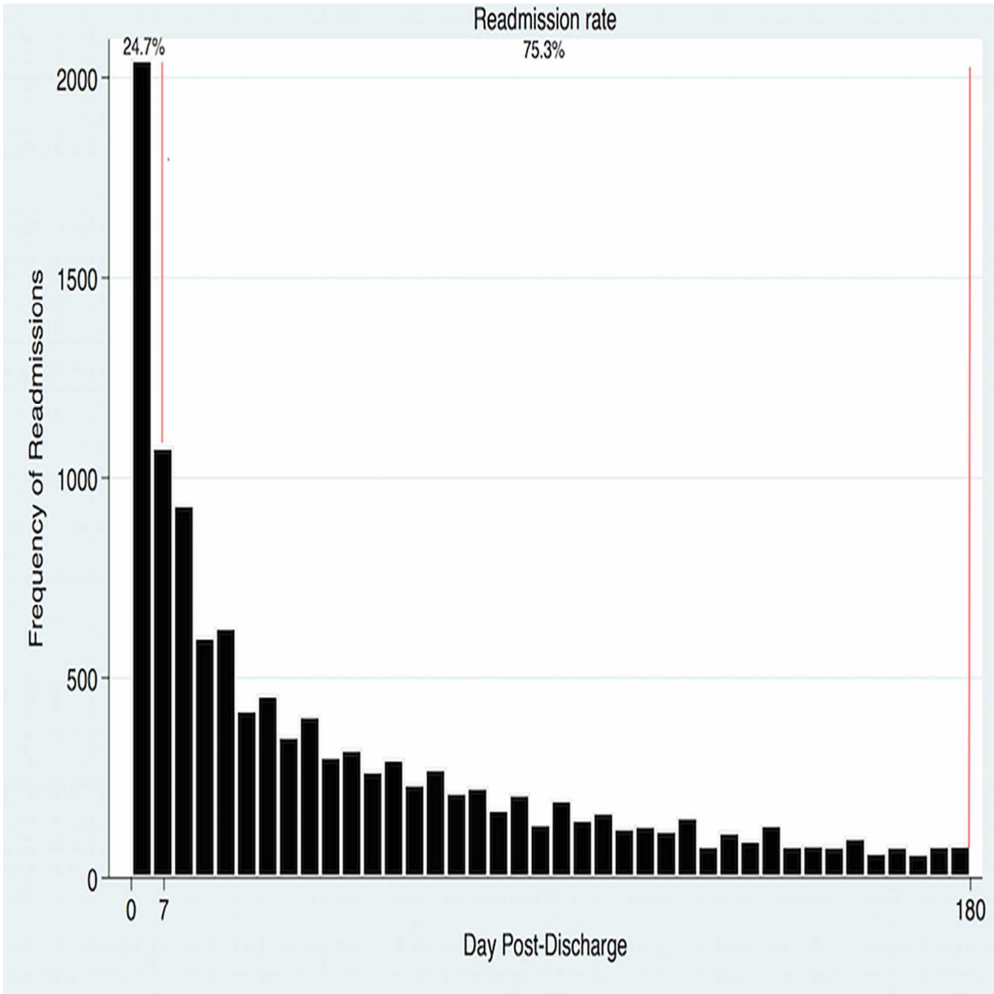
Figure 1 Distribution of readmissions

Figure 2 Cumulative incidence estimate model for readmissions with death as a competing risk. Competing risk regression was used to estimate subdistribution hazard ratio (SHR), 1.17 (95% CI 1.06-1.28). Model adjusted for covariates-age, sex, charlson index and length of hospital stay.



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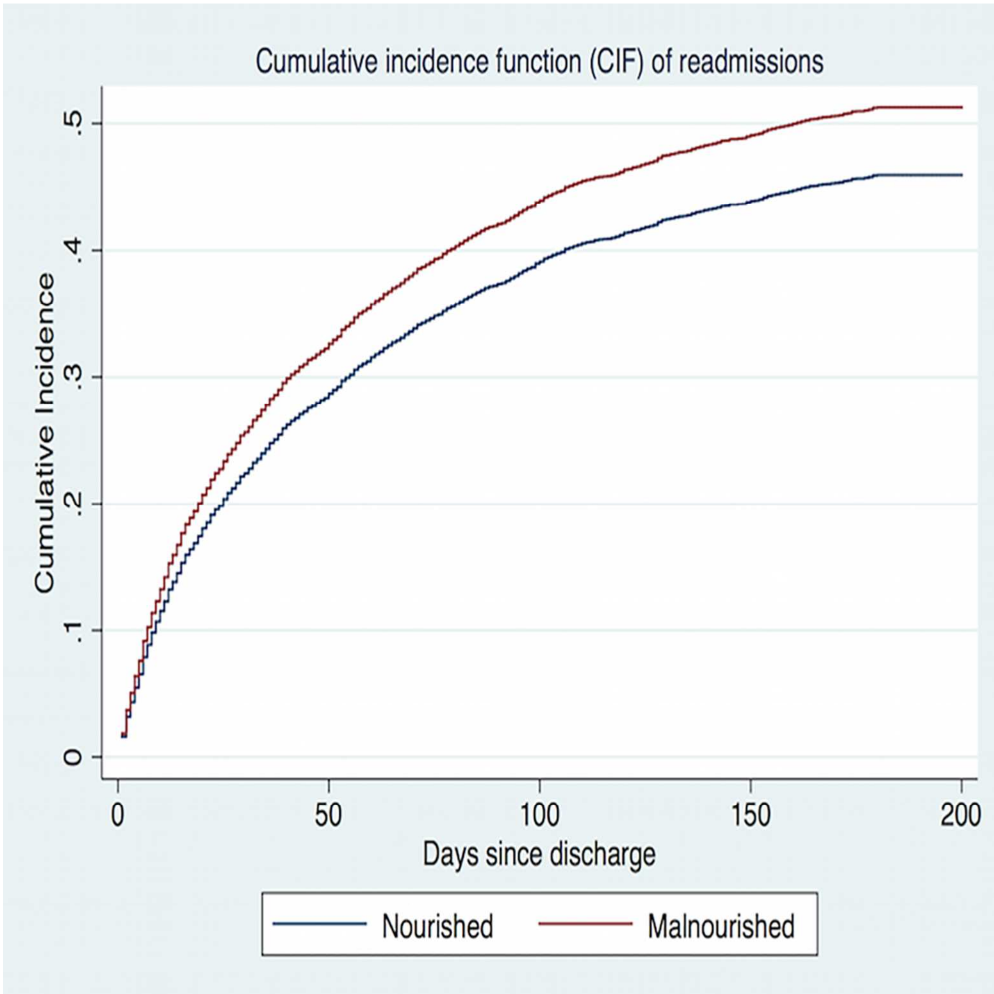

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90x90mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page 1 and page 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pages 4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 7
Methods			
Study design	4	Present key elements of study design early in the paper	Pages 7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Pages 7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pages 8-9
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pages 8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 9-10
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pages 10-11, Table 1
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A information in Table 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pages 10-11 and Tables 1-2
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	Pages 12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 11-13, Table 2
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pages 14-15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.