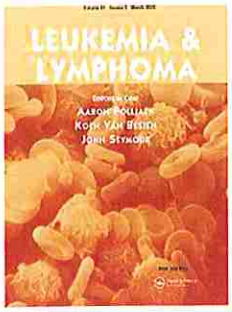

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ORIGINAL ARTICLE



# Trends in myeloma relative survival in Queensland by treatment era, age, place of residence, and socioeconomic status

Matthew Harwood[a], Nathan Dunn[b], Julie Moore[b], Peter Mollee[a,c] and Greg Hapgood[a,c]

[a]Department of Haematology, Princess Alexandra Hospital, Brisbane, Australia; [b]Queensland Cancer Control Analysis Team, Queensland Health, Brisbane, Australia; [c]University of Queensland, Brisbane, Australia

**ABSTRACT**

Relative survival (RS) in myeloma has improved in younger but not older patients (≥80 years) with treatment advances. Whether place of residence or socioeconomic status (SES) affect RS is unknown. We used the Queensland cancer registry to calculate the five-year RS of myeloma patients diagnosed between 1982 and 2014. This period was divided into three eras: (1) 1982–1995 chemotherapy alone; (2) 1996–2007 autologous stem cell transplantation; (3) 2008–2014 novel agents (proteasome inhibitors and IMIDs). 6025 patients were diagnosed from 1982 to 2014. RS improved across eras: (1) 30% vs. (2) 43% vs. (3) 53% ($p < .001$ (2) vs. (1); $p < .001$ (3) vs. (2)). RS improved across all age groups, including patients ≥80 years. Patients with disadvantaged SES (39% vs. affluent 46%; $p < .001$) and rural patients (40% vs. urban 45%; $p < .001$) had an inferior RS. RS has improved across all ages with treatment advances.

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Relative survival; myeloma; novel agents; place of residence; socioeconomic status

## Introduction

Myeloma is an incurable plasma cell neoplasm that accounts for 1% of all malignancies and 10% of all hematological malignancies [1]. Myeloma is defined by the presence of >10% plasma cells in the bone marrow or a plasmacytoma on tissue biopsy, typically with a monoclonal protein in blood and/or urine [1]. Myeloma has a clinical spectrum ranging from asymptomatic (smouldering) myeloma with no end-organ damage to symptomatic myeloma with end-organ damage defined by 'CRAB' features directly related to myeloma: hypercalcemia, *r*enal impairment, *anemia*, and *b*one lesions [2]. Prognosis is determined by the Revised International Staging System (R-ISS) which incorporates cytogenetic data to stratify patients into three stages with estimated five-year overall survival (OS) rates of 82%, 62%, and 40%, respectively [3].

The myeloma treatment landscape has evolved considerably in recent decades. Treatment is aimed at achieving a complete response and maintaining remission. Melphalan was one of the first drugs to improve OS when added to prednisone in the 1960s [4]. Over the next three decades, various combination chemotherapy regimens were developed but none improved OS compared to melphalan and prednisolone [5]. The next major advance was the introduction of autologous stem cell transplantation (ASCT) for younger patients with myeloma, typically <65 years [6]. This was widely introduced in Queensland in the mid-1990s. In 2007, the proteasome inhibitor (PI) bortezomib was funded by the Australian Pharmaceutical Benefits Scheme (PBS) for relapsed disease and then first-line in 2012. Further treatment advances came with immunomodulatory drugs (IMIDs) when thalidomide was added to the PBS in 2008 for first-line treatment and relapsed disease followed by lenalidomide for relapsed disease in 2009 and first-line treatment in 2017.

Several international population-based registry studies have reported improvements in relative survival (RS) in recent decades [7–10]. A consistent finding has been improvements in RS in younger patients but no significant improvements in elderly patients (i.e. >80 years). These improvements have been directly linked to the introduction of ASCT and, more recently, PIs and IMIDs [7–10]. To our knowledge, there is no large-scale population-based Australian study exploring changes in RS with recent treatment advances.

A number of studies have demonstrated variation in cancer survival between rural and urban regions [11–16]. While inferior survival rates for rural patients

CONTACT Greg Hapgood greg.hapgood@health.qld.gov.au Department of Haematology, Princess Alexandra Hospital, 199 Ipswich Road, Woolloongabba, Brisbane 4102, Australia

with solid tumors is a common theme in the literature, less data is available for patients with myeloma. Lower socioeconomic status (SES) has been reported as a predictor of inferior survival in cancer [14,17–19]. Whether place of residence or SES impact upon outcomes for patients with myeloma in Australia is unknown.

The primary objective of this study was to evaluate the RS of patients with myeloma to determine if outcomes have improved with treatment advances. The secondary objectives were to evaluate RS based on place of residence (urban vs. rural) and SES to determine if reported differences in solid cancers exist in myeloma patients in Queensland.

## Methods

We performed a retrospective population-based analysis of all patients diagnosed with myeloma in Queensland between 1982 and 2014. Myeloma cases were defined as per ICD-10 code C90.0. Plasma cell leukemia (C90.1), extramedullary plasmacytoma (C90.2), and solitary plasmacytoma (C90.3) were not included. Data analyzed in our study were obtained from the Oncology Analysis System (OASys), the population-based online reporting tool for cancer incidence and outcomes in Queensland. OASys is operated by Cancer Alliance Queensland, which includes the Queensland Cancer Registry (QCR) and the Queensland Cancer Control Analysis Team (QCCAT). QCR records of cancer diagnoses for patients living in Queensland since 1982 are consolidated by QCCAT into a single database, the Queensland Oncology Repository (QOR), the basis of OASys.

Demographic information included age at diagnosis, gender, region (remoteness), and SES of residence. Remoteness was categorized according to Australian Standard Geographical Classification (ASGC) at diagnosis [20], and grouped into urban (Brisbane, Gold Coast, Townsville) and rural categories (inner/outer regional, remote, very remote regions). SES was classified according to the Socio-Economic Indexes For Areas (SEIFA) Index of Relative Socio-economic Disadvantage (affluent, middle, disadvantaged) which is based on the characteristics of the area of residence (primarily census data on income, education, employment, occupation, and housing) [21]. The study period was divided into eras to assess the impact of treatment changes on survival: period 1 – chemotherapy alone 1982–1995; period 2 – 1996–2007 ASCT; period 3 – 2008–2014 novel agents (PI and IMIDs). Local ethics and governance approval was obtained (HREC17/QPAH/696).

### Statistical analysis

In the primary analysis, we estimated RS employing a cohort approach and the Ederer II method [22]. RS is defined as the ratio of the number of observed deaths in a cancer cohort to the observed number of deaths in a cohort of individuals without cancer. We compared the mortality of myeloma patients with that of the general population using age-, sex-, and calendar period-generated (expected) mortality rates from Queensland life tables in OASys compiled from Australian Bureau of Statistics population and death data [23]. The influence on RS of gender, place of residence (urban vs. rural), SES of residence, age, and year of diagnosis (treatment era) was assessed in univariate and multivariate analyses with a full maximum likelihood approach [24,25]. Variables with a $p$-value $<.2$ were included in the multivariate analysis using a backwards selection model. OS was defined as the time from diagnosis until death from any cause and was measured using the Kaplan–Meier method. Statistical analyses were performed using STATA/IC 14.0 (StataCorp, College Station, TX).

## Results

### Patient characteristics

A total of 6025 patients (males = 3437, females = 2588) diagnosed with myeloma in Queensland between 1982 and 2014 were included (Table 1). The median age at diagnosis was 70 years (interquartile range 61–78 years). Males comprised 57.1% of all patients. A total of 3973 (65.9%) of patients lived in urban areas at the time of diagnosis. SES was classified as affluent ($n = 950$, 15.8%), middle ($n = 3695$, 61.3%) or disadvantaged ($n = 1373$, 22.8%). Gender, age, place of residence, and SES did not appear to differ across treatment eras.

### Relative survival analysis according to treatment eras

There was a significant improvement in RS across treatment eras in univariate analysis (Table 2). Five-year RS for all patients improved significantly from 30% (95% CI 28–33) in 1982–1995 to 43% (95% CI 41–45) in 1996–2007 to 53% (95% CI 51–56) ($p < .001$ for 1982–1995 vs. 1996–2007 comparison, $p < .001$ for 1996–2007 vs. 2008–2014 comparison). In the multivariate analysis, RS was significantly better for the eras

**Table 1.** Patient characteristics: gender, age, place of residence, and socioeconomic status.

| | Era 1 (1982–1995) | Era 2 (1996–2007) | Era 3 (2008–2014) | Total |
|---|---|---|---|---|
| Gender | | | | |
| Male | 858 (56.2%) | 1347 (56.1%) | 1232 (58.7%) | 3437 (57.1%) |
| Female | 668 (43.8%) | 1053 (43.9%) | 867 (41.3%) | 2588 (42.9%) |
| Age | | | | |
| <60 | 339 (22.1%) | 535 (22.3%) | 441 (22%) | 1315 (21.8%) |
| 60–69 | 395 (25.9%) | 581 (24.2%) | 597 (28.4%) | 1573 (26.1%) |
| 70–79 | 499 (32.7%) | 714 (29.8%) | 588 (28%) | 1801 (29.9%) |
| >80 | 293 (19.2%) | 570 (23.7%) | 473 (22.5%) | 1336 (22.2%) |
| Residence | | | | |
| Urban | 1020 (66.8%) | 1591 (66.3%) | 1362 (64.9%) | 3973 (65.9%) |
| Rural | 504 (33%) | 809 (33.7%) | 737 (35.1% | 2050 (34%) |
| Unknown | 2 (0.1%) | 0 | 0 | 2 (0.1%) |
| Socioeconomic status | | | | |
| Affluent | 269 (17.6%) | 381 (15.9%) | 300 (14.3%) | 950 (15.8%) |
| Middle | 905 (59.3%) | 1470 (61.3%) | 1320 (62.9%) | 3695 (61.3%) |
| Disadvantaged | 349 (22.9%) | 545 (22.7%) | 479 (22.8%) | 1373 (22.8%) |
| Unknown | 3 (0.2%) | 4 (0.2%) | 0 | 7 (0.1%) |

**Table 2.** Relative survival based on year of diagnosis (treatment era).

| | Era 1 (1982–1995) | | Era 2 (1996–2007) | | Era 3 (2008–2014) | | Total | |
|---|---|---|---|---|---|---|---|---|
| | 5yr RS | 95% CI | 5yr RS | 95% CI | 5yr RS | 95% CI | 5yr RS | 95% CI |
| All patients | 0.30 | 0.28–0.33 | 0.43 | 0.41–0.45 | 0.53 | 0.51–0.56 | 0.43 | 0.42–0.45 |
| Age group | | | | | | | | |
| <60 years | 0.42 | 0.37–0.48 | 0.62 | 0.58–0.67 | 0.70 | 0.65–0.75 | 0.60 | 0.57–0.63 |
| 60–69 years | 0.31 | 0.26–0.36 | 0.53 | 0.48–0.57 | 0.65 | 0.60–0.69 | 0.52 | 0.49–0.55 |
| 70–79 years | 0.26 | 0.22–0.31 | 0.31 | 0.27–0.35 | 0.47 | 0.42–0.52 | 0.35 | 0.32–0.38 |
| > =80 years | 0.13 | 0.08–0.20 | 0.21 | 0.17–0.26 | 0.23 | 0.17–0.29 | 0.21 | 0.18–0.24 |
| SES | | | | | | | | |
| Affluent | 0.35 | 0.28–0.41 | 0.43 | 0.37–0.49 | 0.58 | 0.50–0.65 | 0.46 | 0.42–0.49 |
| Middle | 0.30 | 0.27–0.34 | 0.43 | 0.40–0.46 | 0.54 | 0.50–0.57 | 0.44 | 0.42–0.46 |
| Disadvantaged | 0.25 | 0.19–0.30 | 0.40 | 0.35–0.44 | 0.48 | 0.43–0.54 | 0.39 | 0.36–0.42 |
| Place of residence | | | | | | | | |
| Urban | 0.31 | 0.28–0.34 | 0.45 | 0.42–0.47 | 0.55 | 0.52–0.59 | 0.45 | 0.43–0.47 |
| Rural | 0.27 | 0.23–0.32 | 0.38 | 0.34–0.42 | 0.49 | 0.45–0.54 | 0.40 | 0.37–0.42 |

RS: relative survival; CI: confidence interval; SES: socioeconomic status.

**Table 3.** Multivariate analysis of relative survival.

| | HR | 95% CI | *p*-value |
|---|---|---|---|
| Era | | | |
| 1982–1995 | – | | – |
| 1996–2007 | 0.62 | 0.57–0.68 | <.001 |
| 2008–2014 | 0.46 | 0.41–0.51 | <.001 |
| Residence | | | |
| Urban | 0.85 | 0.78–0.92 | <.001 |
| Rural | – | | – |
| SES | | | |
| Affluent | – | | – |
| Middle | 1.04 | 0.93–1.17 | .476 |
| Disadvantaged | 1.23 | 1.07–1.40 | .004 |
| Age group | | | |
| <60 | – | | – |
| 60–69 | 1.32 | 1.17–1.49 | <.001 |
| 70–79 | 2.17 | 1.94–2.43 | <.001 |
| 80+ | 3.91 | 3.47–4.40 | <.001 |

HR: hazard ratios; CI: confidence intervals; SES: socioeconomic status.

1996–2007 (HR 0.62, 95% CI 0.57–0.68, $p < .001$) and 2008–2014 (HR 0.46, 95% CI 0.41–0.51, $p < .001$) compared to 1982–1995 (Table 3).

### *Impact of age*

The improvement in RS across each treatment era was also seen in all age groups (Table 2). Five-year RS increased from: 42% (95% CI 37–48) in 1982–1995 to 70% (95% CI 65–75) in 2008–2014 for patients <60 years ($p < .001$); 31% (95% CI 26–36) in 1982–1995 to 65% (95% CI 60–69) in 2008–2014 for patients 60–69 years ($p < .001$); 26% (95% CI 22–31) in 1982–1995 to 47% (95% CI 42–52) in 2008–2014 for patients 70–79 years ($p < .001$); and 13% (95% CI 8–20) in 1982–1995 to 23% (95% CI 17–29) in 2008–2014 for patients ≥80 years ($p < .001$). In the multivariate analysis, RS declined with increasing age (patients ≥80 years HR 3.91, 95% CI 3.47–4.40, $p < .001$ compared to patients <60 years) (Table 3).

### *Impact of gender*

Across all eras, RS was similar between males and females ($p = .47$) and in multivariate analysis gender did not impact RS ($p = .30$).

### *Impact of socioeconomic status*

Improvements in RS were also seen across treatment eras within each SES by univariate analysis (Table 2).

Five-year RS increased from: 35% (95% CI 28–41) in 1982–1995 to 58% (95% CI 50–65) in 2008–2014 for patients classified as affluent ($p < .001$); 30% (95% CI 27–34) in 1982–1995 to 54% (95% CI 50–57) in 2008–2014 for patients classified as middle class ($p < .001$); and 25.0% (95% CI 19–30) in 1982–1995 to 48% (95% CI 43–54) in 2008–2014 for patients classified as disadvantaged ($p < .001$). Five-year RS across all treatment eras for disadvantaged patients was 39% (95% CI 0.36–0.42) vs. affluent patients 46% (95% CI 0.42–0.49) ($p < .001$). In multivariate analysis, there was no significant difference in RS for middle class compared to affluent SES patients (HR 1.04, 95% CI 0.93–1.17, $p = .47$) (Table 3). Conversely, patients classified as disadvantaged had an inferior RS compared to affluent patients (HR 1.23, 95% CI 1.07–1.40, $p = .004$).

### *Impact of place of residence*

Improvements in RS were seen with each treatment era for rural and urban patients (Table 2). Five-year RS increased from: 31% (95% CI 28–34) in 1982–1995 to 55% (95% CI 52–59) in 2008–2014 for urban patients ($p < .001$); and 27% (95% CI 23–32) in 1982–1995 to 49% (95% CI 45–54) in 2008–2014 for rural patients ($p < .001$). Five-year RS across all treatment eras for rural patients was 40% (0.37–0.42) vs. urban patients 45% (0.43–0.47) ($p < .001$). In multivariate analysis, urban patients had improved RS compared to rural patients (HR 0.85, 95% CI 0.78–0.92, $p < .001$) (Table 3).

### *Overall survival analysis*

The results of the OS analysis essentially mimicked those of the RS analysis (Figure 1). Five-year OS improved significantly over the three treatment eras from 25% (95% CI 23–27) in 1982–1995 to 36% (95% CI 34–38) ($p < .001$) in 1996–2007 to 47% (95% CI 44–49) ($p < .001$) in 2008–2014. This OS improvement across treatment eras was consistently seen for all ages (Figure 1(A–D)). Five-year OS increased from: 41% (95% CI 36–46) in 1982–1995 to 69% (95% CI 64–74) ($p < .001$) in 2008–2014 for patients <60 years; 28% (95% CI 24–33) in 1982–1995 to 61% (95% CI 57–65) ($p < .001$) in 2008–2014 for patients 60–69 years; 20% (95% CI 17–24) in 1982–1995 to 40% (95% CI 35–44) ($p < .001$) in 2008–2014 for patients 70–79 years; and 7% (95% CI 4–10) in 1982–1995 to 14% (95% CI 11–19) ($p < .001$) in 2008–2014 for patients ≥80 years. Gender did not significantly impact overall survival with five-year OS for females 37% (95% CI 35–39) vs. 36% (95% CI 35–38) for males ($p = .061$). Urban patients had a superior five-year OS compared to rural patients (38% (95% CI 36–40) vs. 34% (95% CI 32–36) ($p = .005$) (Figure 1(E)). Patients with disadvantaged SES had an inferior five-year OS compared to those of affluent status (33% (95% CI 31–36) vs. 39% (95% CI 36–42) ($p = .002$) (Figure 1(F)).

## Discussion

We examined whether the RS of patients with myeloma in Queensland has improved with treatment advances since 1982. Compared to era 1 (chemotherapy alone), there has been a significant improvement in RS with the introduction of ASCT (era 2) and novel agents (PI/IMIDs) (era 3). Improvements in RS were seen across all age groups. We examined whether there was a survival disadvantage for patients living in rural areas or from a disadvantaged SES. RS was inferior for rural compared to urban patients. Patients from a disadvantaged, but not middle class, SES had an inferior RS compared to affluent patients.

There was a significant improvement in RS with each treatment era across all age groups. Similarly, the OS curves demonstrate an age-gradient with better OS for younger patients and a treatment-gradient with better OS with treatment advances. Era 1 represented alkylator chemotherapy such as melphalan in combination with prednisolone. The introduction of ASCT (era 2) significantly improved RS. Generally, patients must have a good performance status, adequate cardiac and respiratory function and be <70 for ASCT due to potential treatment-related morbidity and mortality. The introduction of ASCT would have contributed to the improvements in RS for patients <70. The most likely explanation for the improvement in RS for era 3 is the introduction of novel agents (IMIDs and PI). All age groups would have benefited from the availability of bortezomib in 2007, thalidomide in 2008, and lenalidomide in 2009 on the PBS in the relapsed/refractory setting. Based on their effectiveness, the introduction of PI and IMIDs resulted in a paradigm shift with their introduction earlier in the disease course.

The RS for elderly patients (≥80) improved across each treatment era. Previous population-based registry studies have not demonstrated similar improvements in elderly patients [8–10]. The improvements in our RS data may have been due to the availability of novel agents and the use of less intensive treatments or the structure of the Australian health care system. Other important advances during this >30-year period occurred in the management of renal failure, supportive care (e.g. anti-infective prophylaxis, granulocyte

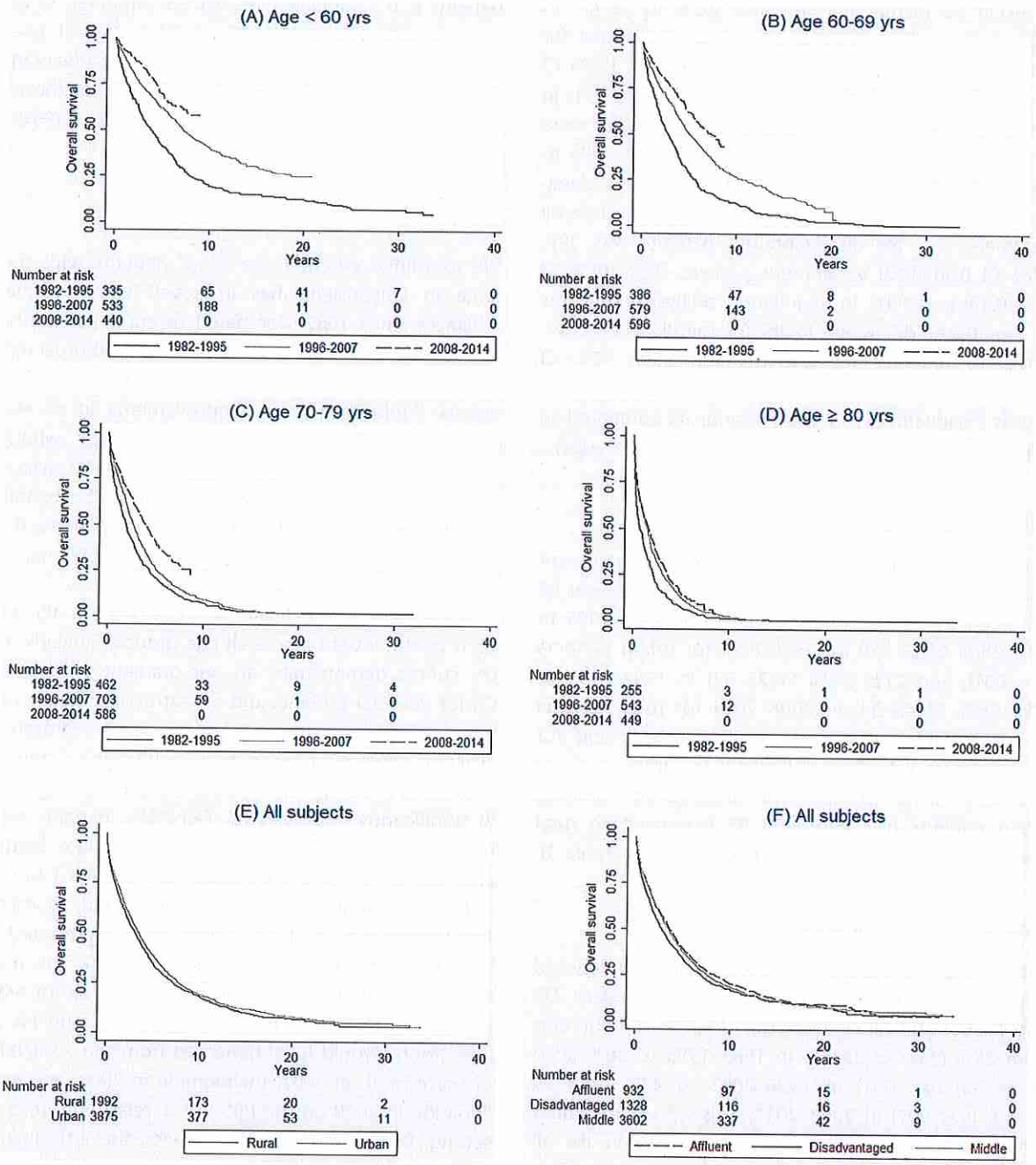


**Figure 1.** (A) Overall survival for myeloma patients <60 years of age. (B) Overall survival for myeloma patients 60–69 years of age. (C) Overall survival for myeloma patients 70–79 years of age. (D) Overall survival for myeloma patients >80 years of age. (E) Overall survival for myeloma patients based on place of residence. (F) Overall survival for myeloma patients based on socioeconomic status.

colony-stimulating factor, anti-nausea medications, intravenous immunoglobulin replacement), venous thromboembolism prophylaxis and the use of intravenous bisphosphonates (e.g. zoledronic acid) to treat hypercalcemia and treat or prevent osteolytic bone disease to avoid pathological fracture.

There was an inferior RS for rural compared to urban patients. This is similar to data regarding inferior survival for other cancers [11–16] with trends to older age, more advanced stage or worse performance status at diagnosis, lower administration rates or delays in receiving treatment as possible reasons for these

differences between rural and urban cancer patients. During this study period, ASCT was only performed at large tertiary referral centers. Rural patients would have had to travel to such centers for ASCT and stay for several months. Outpatient-based parenteral (bortezomib) and oral treatments (lenalidomide, thalidomide) require regular attendance at an outpatient clinic for monitoring. Therefore, during treatment and surveillance, close follow up at a hematology service is required. Place of residence may have influenced the patient's and physician's treatment decisions.

SES was a significant predictor of outcome with an inferior RS demonstrated for disadvantaged compared to affluent patients. Although myeloma treatment is universally available in Australia through a publicly funded health care system, costs are still incurred (e.g. discharge medications, transport, lost employment). Patients from lower socioeconomic groups have lower reported rates of health literacy and higher rates of smoking and obesity which could contribute to higher all-cause mortality [17–19]. Importantly, place of residence and SES remained significant in multivariate testing demonstrating that each was independently predictive of RS.

This analysis has limitations. ICD codes do not distinguish between symptomatic and asymptomatic (smouldering) myeloma, conditions with significantly different prognoses. This is a known limitation in myeloma registry studies [10]. Stage, prognostic information, treatment received and response for individual patients were not available as this information is not collected by OASys. It is unknown if these features were balanced based on place of residence or SES. Place of residence and SES were determined by the patient's address at diagnosis. Some patients from remote areas would have traveled to urban centers for treatment, particularly for urgent treatment.

In our population-based assessment of myeloma patients in Queensland, we found a significant improvement in RS across all age groups with treatment advances from chemotherapy to ASCT to the introduction of novel agents (IMIDs, PIs) during the last 30 years. Rural or disadvantaged SES patients had an inferior RS. All treating medical practitioners should be aware of the benefits of coordinated care in the tertiary setting for rural and/or disadvantaged SES patients to ensure equity of access to effective treatment. Although myeloma is considered incurable, our data demonstrates access to effective treatment improves survival.

## Authorship

All authors had full access to all the data.

## Disclosure statement

M.H., N.D., J.M., G.H.: No relevant disclosures.

P.M.: Amgen, Celgene, and Janssen Myeloma Ad Board member only (no personal fees received). Pfizer Amyloidosis Ad Board member only (no personal fees received).

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