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MicroAbstract

Renal impairment (RI) is common in multiple myeloma (MM) and is associated with poor prognosis. The Australia and New Zealand Myeloma Registry was used to assess >1000 newly diagnosed MM patients, of whom 383 had RI at diagnosis. Patients who underwent autologous stem cell transplant (ASCT) despite RI had improved survival; potential factors for an inferior outcome include suboptimal use of bortezomib and ASCT.

Abstract

Background: Renal impairment (RI) is a common complication of multiple myeloma (MM) and remains a poor prognostic factor despite improved survival with newer therapies.

Patients and Methods: We evaluated baseline characteristics, treatment and outcomes of newly diagnosed MM patients with RI at diagnosis in the Australia and New Zealand Myeloma and Related Diseases Registry over 5 years to April 2018; comparing RI patients (eGFR<60 ml/min) with eGFR≥60. In autologous stem cell transplant (ASCT) analyses, patients ≤70 years and ≥1 year from diagnosis were included.

Results: Overall, 36% of newly diagnosed MM had RI; they were older, had more advanced disease and comorbidities, and worse performance status. Bortezomib-based induction therapy was most commonly used, although administered to fewer RI patients, despite similar response rates. Patients with RI were less likely to receive ASCT; however, recipients had longer progression-free (PFS) and overall survival (OS). Patients with RI had shorter OS and PFS after adjusting for age. In ASCT recipients with RI versus no RI, there was no difference in PFS and OS.

Conclusion: Our findings in 'real world' MM patients with RI confirm that patient-, disease- and treatment-related factors (such as suboptimal bortezomib and ASCT use), and delays in commencing therapy, may contribute to poorer outcomes, and support the use of ASCT in patients with RI.

Introduction

Renal impairment (RI) is a poor prognostic factor in multiple myeloma (MM). Despite improvements in survival with the introduction of novel therapies in recent years, RI remains one of the most common complications with an incidence of 20 to 50% at diagnosis, and approximately 5 to 10% of MM patients are dialysis-dependent.[1-3] The most common cause of RI in MM is cast nephropathy, in which excess light chains form aggregates and casts resulting in tubular blockage and inflammation.[4-6] Other factors include toxic effects of light chains on the basement membranes of glomeruli and proximal tubules, interstitial nephritis, amyloid deposition and plasma cell infiltration, which are further exacerbated by hypercalcaemia, dehydration, hyperuricaemia and nephrotoxic drugs.

Recent developments including the significant efficacy of proteasome inhibitors (PI) in reversing renal failure, and the development of other new agents (such as monoclonal antibodies) are likely to improve disease outcome. The role of autologous stem cell transplant (ASCT) in the transplant-eligible (TE) population with RI has not been definitively established. Current International Myeloma Working Group (IMWG) guidelines indicate level C evidence for ASCT at a reduced melphalan conditioning dose of 140 mg/m^2; however some studies have demonstrated the feasibility and efficacy of full-dose conditioning,[7, 8] despite others recommending dose reduction in some patients[7, 9]. The choice of induction agent(s) in both TE and non-TE patients also varies, and whether combination therapy provides incremental benefit in this high-risk group needs further clarification.

With the overall improvement in prognosis in MM patients,[10] it is crucial to evaluate whether there has been comparable progress in outcomes for this high-risk group with RI. In Australia and New Zealand, treatment protocols usually follow government reimbursement policy, for which combination novel therapies and maintenance therapy (other than thalidomide) are as yet unavailable outside of clinical trials. We investigated current treatment and clinical outcomes for MM patients with RI at diagnosis in Australia and New Zealand using a large, bi-national, real world, prospective clinical registry.

Methods

Data sources

Data for this study were obtained from the Australian and New Zealand Myeloma and Related Diseases Registry (ANZ MRDR). Details regarding the methods of the MRDR have been published separately,[11] and it is registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12618000659202). In brief, the MRDR is a prospective registry established in 2012, of newly diagnosed patients aged 18 years and older with MM, monoclonal gammopathy of undetermined significance (MGUS), smouldering MM, plasma cell leukaemia or solitary plasmacytoma identified by participating sites. The MRDR uses an opt-out consent model. Patient characteristics, co-morbidities, disease characteristics, laboratory parameters and first-line therapy are collected at baseline; then data on therapy, response, disease progression and other outcomes are collected every four months for MM patients and annually for MGUS patients. Periodic linkage is performed with the national death registries in Australia and New Zealand to ensure the quality of survival / mortality outcomes and to provide supplementary data on date and cause of death for any patients lost to follow up.

Patients

For this analysis we included all patients with newly diagnosed MM registered in the ANZ MRDR from 1 February 2013 to 24 April 2018.

Definitions

The Kidney Disease: Improving Global Outcomes (KDIGO) classification for chronic kidney disease[12] was used to classify renal function as recommended by the IMWG.[6] The eGFR reported in the registry is generally derived from laboratory results using the CKD-EPI formula which has been recommended for use in Australasian laboratories since 2012.[13] RI was defined as eGFR < 60mL/min/1.73m^2. Patient-, disease- and treatment-related factors were compared. Standard IMWG criteria for response were used.[14]

We classified transplant-eligible (TE) patients as those aged ≤ 70 years at diagnosis; the analyses only included patients with diagnosis date ≥ 1 year prior to data extraction (to allow time for transplant) and who had follow-up data.

Statistical analysis

Summary statistics are presented as proportion, mean (standard deviation) or median (inter-quartile range) as appropriate. Comparisons between groups were made using the Chi-square, Wilcoxon Rank sum, or Kruskal-Wallis test as appropriate. OS and PFS were calculated using Kaplan-Meier survival analysis, with censoring on death. The proportional hazards assumption was tested and all analyses were done using Stata version 15.1 (StataCorp LLC, Texas, USA).

Results

Patient and disease characteristics

Of 1251 patients with MM on the MRDR, 1069 (85%) had eGFR available at diagnosis (Figure 1), and these 1069 patients were used in the RI analyses. Of these patients, 36% had RI (eGFR < 60 mL/min/1.73m^2): 24% had eGFR 30-59 mL/min; 6% had eGFR 15-29 mL/min; and eGFR was <15 mL/min in 6% of patients.

Compared with patients who had normal renal function, patients with RI at diagnosis were older (72 v 65 years, p<0.001) and had more advanced stage disease (International Staging System (ISS) III: 66 v 13%, Revised-ISS III: 34 v 5%, p<0.001). See Table 1. Since RI is one of the defining criteria for ISS stage (both ISS and R-ISS) and beta-2 microglobulin (β2M) is affected by renal function, we reviewed the other staging criteria to determine whether RI alone was the reason for increased stage in this group. The R-ISS components of high-risk FISH and LDH were compared, showing that 57% with RI versus 44% with no RI had these high-risk changes (p=0.01). Patients with RI had a higher LDH (205 U/L, 164-261) compared with no RI (186 U/L, 152- 234) (p<0.001) which is likely to reflect myeloma cell proliferation. High-risk FISH abnormalities were present in 31% of patients with RI, and 24% with no RI (p=0.07).

Patients with RI had a worse performance status (ECOG 2-4: 30 v 18%, p<0.001) and more co-morbidities: more patients with RI had diabetes (15 v 9%, p=0.005), cardiac disease (15 v 8%, p<0.001) and abnormal liver function tests (2.6 v 0.7%, p=0.01). There was no difference in the prevalence of pulmonary disease or peripheral neuropathy between the two groups (See Table 1).

In disease manifestations other than RI defining MM activity, hypercalcaemia (10 v 4%, p=0.001) and anaemia (43 v 16%, p<0.001) were both more common in patients with RI; however fewer patients with RI had bone lesions (53 v 67%, p<0.001).

Treatment and response

The time from diagnosis to commencement of induction therapy was shorter in patients with RI (median 15 days; IQR 13 to 18 days, 90th centile 60 days) compared with no RI (25 days; 22-27, p<0.001). Bortezomib-based therapy was most commonly used for induction in all patients, however it was given to fewer patients with RI (80% v 88%, p=0.002, see Table 2). Carfilzomib-based therapy was used in 2.2% of patients with RI and 0.5% of non-RI patients. Overall the percentage of patients who received a PI of either bortezomib or carfilzomib was still lower in patients with RI (82.5%) compared with non-RI (88.3%) (p=0.013). Although carfilzomib is not approved for first line treatment of MM in our jurisdiction, a clinical trial on carfilzomib/dexamethasone was in progress specifically for RI patients during the period of data collection. Contrary to the understanding that PIs are particularly effective in MM patients with RI, there was no obvious factor identified for the lower proportion of RI patients receiving a PI as first line therapy compared with other treatments. We investigated the possibility that parenteral treatment of bortezomib may be less favoured in older patients compared with oral treatment, but this was not the case as a greater proportion of patients with RI over 70 years compared with no RI received bortezomib [75% (145/193) v 69% (120/173)], with the reverse finding in patients 70 years or under [86% (143/166) v 94% (448/475)]. Response rates (≥PR) to bortezomib in both groups were similar (≥PR rate 81% in RI v 84% in no RI,

p=0.28), and there was also no statistically significant difference in response to thalidomide-based therapy between groups (≥PR: RI 48% v no RI 67%, p=0.12).

Fewer TE patients (defined in Methods) with RI received ASCT (62 v 78%, p<0.001) and ASCTs were performed at all levels of renal function including in patients with severe RI (eGFR <30 mL/min). The proportion of patients transplanted at each eGFR level was: eGFR 30-59 mL/min (63%), eGFR 15-30 mL/min (58%) and eGFR <15 mL/min (61%). Standard dose melphalan (200mg/m^2) was given for ASCT conditioning in 72 v 93% of patients with RI v no RI, and lower dose melphalan (140mg/m^2) in 27 v 5% of RI v no RI (Table 2). Among patients who were <70 years and had >1 year follow-up, those who received ASCT compared with those who did not receive ASCT, were younger (59.8 yrs vs 65.0 yrs, p<0.001), had better performance status, a higher median eGFR (81 v 68 ml/min; p<0.001); but there was no significant difference in R-ISS categories (Supplementary data; Table 1).

Although the age of 70 is commonly accepted within our jurisdiction as a threshold for transplant eligibility, we specifically reviewed the age group 65-70 years to determine whether patients in this group closest to the threshold were less likely to receive an ASCT if they had RI. While for both patients with and without RI, a lower proportion of older patients between 65 and 70 years were transplanted compared to patients under 65, the difference appeared to be more pronounced in the RI group (RI: 44 v 71%; no RI: 61 v 85%).

Of 383 patients with RI at diagnosis, 18 were dialysed close to diagnosis, however two received dialysis for medical problems unrelated to myeloma. Of the remaining 16 patients, 94% (15/16) had eGFR< 15 mL/min at diagnosis, and 88% (14/16) received bortezomib first-line chemotherapy, with ≥PR of 75% (9/12). Only 38% (3/8) versus 64% (87/137) of dialysed versus non-dialysed patients with RI underwent ASCT (p=0.14), however, there was no statistically significant difference in treatment, response, OS or PFS between groups (p≥0.06), which may be due to lack of power given the low

numbers. Of the dialysed patients, 7/16 (44%) became dialysis independent within three months of commencement.

Plasma exchange was administered in 1.0% of patients with RI versus 1.7% in no RI (p=0.36).

Progression-free and overall survival

Median patient follow-up was 19 months. PFS and OS were reduced in patients with RI: median PFS was 25 versus 33 months (p<0.001), and median OS 47 months for RI, versus not reached; p<0.001 (Table 2). For patients with RI, 75% were alive at 23 (18-27) months versus 38 (35-43) months for no RI (Figure 2). After adjustment for age, the hazard ratios (HR) for OS and PFS were 0.62 (95% CI 0.47-0.81, p<0.001) and 0.74 (95% CI 0.61-0.91, p=0.004), respectively. After adjustment for other co-morbidities – moderate to severe cardiac disease and ECOG performance status - in addition to age, the hazard ratios (HR) for OS and PFS were 0.72 (95% CI 0.52-0.99, p=0.045) and 0.80 (95% CI 0.63-1.03, p=0.087), respectively.

PFS and OS were compared across all stages of chronic kidney disease in Figure 2C and D indicating an increasing trend in survival time with better renal function.

In patients with RI receiving bortezomib versus thalidomide-based first line chemotherapy (n=285 v 32, those receiving both [n=3] were excluded) there was no difference in PFS (HR 0.78, 95%CI 0.48-1.27, p=0.32) or OS (HR 0.89, 95%CI 0.49-1.61, p= 0.70).

TE patients with RI who received ASCT had a longer OS (HR 0.41, 95%CI 0.19-0.90, p=0.03) and PFS (HR 0.54, 95% CI 0.32-0.93, p=0.03) compared with those who did not receive an ASCT (Figure 3).

In ASCT recipients, there was no difference in PFS (HR 0.97, 95%CI 0.62-1.50, p=0.87) or OS (HR 0.82, 95%CI 0.41-1.62, p=0.57) between patients with and without RI (Figure 4).

Patients with RI who received melphalan 200mg/m^2 had a shorter median PFS than those who received 140mg/m^2 (31 months v not reached, p=0.05; HR 0.43, CI 0.18-1.04, p=0.06), however there was no significant difference in OS or response to therapy (≥PR) between groups.

Of 491 patients who were ≤70 years and received an ASCT, only 201 patients had data available on maintenance therapy. Of these patients 151/201 (75.1%) received thalidomide, the only agent approved for maintenance in our jurisdiction: 93 (46.2%) received thalidomide alone, 58 (28.9%) received thalidomide plus prednisolone, 5(2.5%) received prednisolone alone. Other maintenance therapies including bortezomib, lenalidomide, panobinostat were administered in the remaining 45 patients, of which the majority (33/45[73%] or 33/201[16%] of the total cohort with maintenance data) was administered in clinical trials.

Overall, 119 patients have died in the RI group (31%) and 118 patients in no-RI (17%). There was no significant difference in the median number of chemotherapy regimens administered prior to death.

As diabetes is the most important cause of RI in the Australian population[15], we evaluated the possible effect of diabetes requiring treatment on myeloma outcome. We found no impact on PFS, OS, or response to first-line therapy (p≥0.8). While a larger proportion of patients with RI had diabetes than no RI (Table 1), in patients with RI, there was no significant difference in outcome between those with and without diabetes [≥PR 80.5% v 80.6%, p=0.99; PFS 25.0 (CI 19.5 – 34.4) v 24.5 (20.2-28.5) months, p=0.89; OS 38.7 (30.2 – not reached) v. 47.9 (43.4-57.8) months, p=0.80]. In the Australian community the two other major causes of renal failure are glomerulonephritis and hypertension, for which current data in our registry do not enable an accurate assessment of their impact.

Discussion

Key findings

In our analysis of 1069 newly diagnosed MM patients from the ANZ MRDR, we found 36% had RI at diagnosis and this was associated with older age, presence of co-morbidities, worse performance status and higher-risk disease. Bortezomib-based therapy was the most common first-line treatment in RI, although this was used less frequently compared with those without RI, despite similar response rates. Patients with RI had a shorter OS and PFS compared with patients without RI after adjusting for age. Patients with RI were less likely to receive an ASCT; however those with RI who were transplanted had a longer PFS and OS than those who were not. In addition, OS and PFS were similar in those who received ASCT irrespective of the presence of RI.

It is clear from previous studies that in the overall MM population, PFS and OS are superior for TE compared to NTE patients[16]. In our study, the improved PFS and OS for patients with no RI compared with RI remained significant after adjustment for age. However, as age, co-morbidities and performance status all constitute important eligibility criteria for ASCT, it is not surprising that when PFS and OS were adjusted for all these factors, the differences between RI and no RI became less pronounced, as this adjustment would mitigate the impact of ASCT on prognosis.

In clinical trials of novel drugs or regimens in MM, patients with RI are often excluded, which limits our understanding of their response to treatment and outcomes. This cohort is from a binational registry of over 1250 myeloma patients with eGFR available from 85% of patients, providing the opportunity for assessment of the incidence, underlying factors, treatment and outcomes in newly diagnosed MM with RI in a large “real world” population.

Comparison with other studies

We show that patients with RI represented a third of newly diagnosed MM in the MRDR and that RI is associated with a poor prognosis[17-19], consistent with other findings[6, 20, 21]. MM patients with RI

were older, had a higher prevalence of advanced stage disease and higher LDH (correlated with myeloma cell proliferation, despite a lower prevalence of bone lesions), and shorter PFS and OS.

Since it is clear that PI have particular effectiveness in RI in MM,[22] it is of interest to note that fewer RI patients in this population received them compared to the cohort without RI. We investigated the possibility that age may be a factor favouring oral immunomodulator therapy in the older age group but this was not the case. It is also possible that the RI was considered by the treating doctor not to be due to MM in some of these patients, and hence a PI was not utilised in the initial treatment. Furthermore, there was no difference in the best clinical response between patients with RI versus no RI either in bortezomib-based or thalidomide-based treatment. In addition, for patients with RI receiving bortezomib versus thalidomide-based first line chemotherapy, there was no significant difference in PFS or OS ($p>0.32$), however the number of patients on thalidomide was low (n=32). Before the era of 'novel agents', RI in MM was associated with poor prognosis.[23-25] Since then, evidence suggests that the reversal of RI may be associated with an improvement in prognosis[26-28] with novel agents playing a significant role.[10, 29] However, as long-term follow-up data on renal response is not routinely collected on all MRDR patients, it was not possible to ascertain the difference in efficacy of each treatment in reversing RI. Given the importance of prompt initiation of treatment in patients with RI, and the established link between reversal of RI and prognosis, it is pleasing to see that the median time from diagnosis to treatment for RI (median 15 days, IQR 13-18) is significantly lower though still considered clinically suboptimal; it is of even greater concern that 10% of RI patients started treatment after 60 days.

This study has shown that ASCT is commonly performed in Australian and New Zealand patients with RI and at all levels of renal function, however the rate of ASCT is still lower in RI than in patients with normal renal function (62% vs 78%, $p<0.001$). This was particularly the case in patients close to the age threshold of transplant eligibility of 65-70 years, where the difference was 44% vs 71% for RI vs no RI. A long-standing concern is the reported increased morbidity and mortality of ASCT in patients

with RI, attributed to the possible accumulation of melphalan, the most common conditioning agent which requires renal clearance. The evidence for ASCT in MM patients with RI is heterogeneous. A recent CIBMTR review[8] showed that for patients who received ASCT no difference was seen in PFS or OS for patients with different levels of renal function. The study did not include a comparison with non-transplanted patients. The same CIBMTR report did not show any difference in outcomes between full-dose (200 mg/m^2) and reduced-dose (140 mg/m^2) conditioning, except in a group with eGFR 30-59 mL/min, in whom a higher dose of melphalan (200 mg/m^2) was associated with improved PFS. In contrast, a clinical trial of ASCT in patients with eGFR <30 ml/min showed that only reduced-dose melphalan conditioning of 140 mg/m^2 led to an improved PFS compared with historical controls with normal renal function.[30]

Our study showed that patients with RI who underwent ASCT were more likely to have a longer PFS and OS than those who did not receive ASCT. Furthermore, in patients who underwent ASCT, there was no difference in PFS and OS between patients with and without RI. These results support the use of ASCT in TE patients with RI and with appropriate performance status. However, we found that a significantly lower proportion of patients with RI received ASCT compared with those with no RI. The worse ECOG status of patients with RI (Table 1) may have accounted for TE patients with RI not receiving ASCT. In addition, in our cohort, a significantly higher percentage of patients with RI v no RI (27 v 5%) are administered the lower melphalan dose (140 mg/m^2). Patients with RI who received melphalan 200mg/m^2 had a shorter PFS than those on 140 mg/m^2 (31 months v not reached, p=0.05; HR 0.43, CI 0.18-1.04, p=0.06), however there was no significant difference in OS or response to therapy (≥PR) between groups. Thus, as in the CIBMTR study, we saw no clear advantage for either of the two doses of melphalan conditioning.

At the time of data collection, the only funded maintenance treatment available in our jurisdiction was thalidomide. Of patients ≤70 years who received an ASCT and had data on maintenance therapy (n=201), three-quarters received thalidomide, and the remainder were given numerous therapies

including small numbers treated with bortezomib, lenalidomide and panobinostat maintenance, predominantly on clinical trials. Due to the lack of maintenance therapy data in over half the transplanted patients and the heterogeneity of regimens, we cannot compare strategies and their impact on disease; rather we can present an overall view of maintenance therapy use in our community.

Of 383 patients with RI, 16 were dialysed for reasons related to their myeloma disease. There was no significant difference in treatment, response, OS or PFS between dialysed versus non-dialysed groups ($p \geq 0.06$), which may be due to lack of power with the low numbers. However, it was pleasing to see that of the dialysed patients, 7/16 (44%) became independent of dialysis within 3 months of commencement.

While we are not able to determine the cause of shortened OS definitively from the registry data for patients with RI; potential contributing factors include suboptimal use of PI and ASCT. There was no evidence of increased treatment-related mortality: cause of death was disease-related in 87% of patients with RI and 85% without RI. It is likely that reduced efficacy of treatment leading to earlier relapse in patients with RI (as seen in the shorter PFS) is the main cause of the reduced OS rather than treatment-related or other causes of mortality.

Strengths and limitations

The use of a binational clinical registry with 5 years of prospective data collection from 23 institutions representing metropolitan and regional healthcare underlies the strength and generalisability of our findings. Limitations include the observational nature of the study, missing data on baseline renal function in 15% of patients, the lack of data on the precise cause of renal impairment (MM or non-MM related) and the absence of follow-up data for renal function to assess renal outcomes.

Conclusion

In summary, these findings confirm the higher risk of MM in the presence of RI at diagnosis, with a shortened PFS and OS. While patient characteristics such as more advanced age, poorer ECOG status and higher tumour burden may be important factors, our findings also reveal possible treatment-related factors such as delay in commencing treatment, with 10% of RI patients starting treatment after 60 days, as well as a suboptimal utilisation of bortezomib and ASCT as possible contributors. Our findings clearly support the use of ASCT in MM patients with RI to achieve better OS and PFS, with no advantage of either full-dose or reduced-dose melphalan conditioning. Although follow-up data on renal response was not available, just over 40% of patients who were dialysed due to MM became dialysis-independent within three months of treatment. Given our understanding of the importance of consolidation and maintenance in both TE and non-TE patients with normal renal function, future review of these additional strategies will provide useful information. Furthermore, the introduction of induction therapies such as the newer PI, immunomodulatory drugs and monoclonal antibodies will also likely change the outlook for this group of high-risk patients.

Clinical practice points

- Patients diagnosed with MM frequently have RI (36% of MM in our cohort) which is known to be associated with adverse outcomes.
- In a large real world MM cohort, this study confirms the adverse prognostic impact of RI on MM patients, and describes the factors contributing to adverse outcomes.
- Treatment-related factors that may have contributed to adverse outcomes are a prolonged time to induction therapy, and suboptimal utilisation of bortezomib and ASCT.
- Over 40% of patients who were dialysed due to MM at diagnosis became dialysis-independent within three months of treatment.
- Results suggest that the increased use of ASCT in appropriate patients, PIs for induction, and a reduction in delays to treatment could lead to improved prognosis in MM with RI.

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References

1. Goldschmidt H, Lannert H, Bommer J, Ho AD. Multiple myeloma and renal failure. *Nephrology Dialysis Transplantation.* 2000; 15:301-304.

2. Laforet M, Jourde-Chiche N, Haddad F, et al. Evolution in the treatment of multiple myeloma and impact on dialysis independence: data from a French cohort from 1999 to 2014. *Blood Cancer J.* 2016; 6:e409.

3. Yadav P, Cook M, Cockwell P. Current Trends of Renal Impairment in Multiple Myeloma. *Kidney Dis (Basel).* 2016; 1:241-257.

4. Huang ZQ, Sanders PW. Biochemical interaction between Tamm-Horsfall glycoprotein and Ig light chains in the pathogenesis of cast nephropathy. *Lab. Invest.* 1995; 73:810-817.

5. Sengul S, Zwizinski C, Simon EE, Kapasi A, Singhal PC, Batuman V. Endocytosis of light chains induces cytokines through activation of NF-kappaB in human proximal tubule cells. *Kidney Int.* 2002; 62:1977-1988.

6. Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment. *J. Clin. Oncol.* 2016; 34:1544-1557.

7. El Fakih R, Fox P, Popat U, et al. Autologous Hematopoietic Stem Cell Transplantation in Dialysis-Dependent Myeloma Patients. *Clin. Lymphoma Myeloma Leuk.* 2015; 15:472-476.

8. Mahindra A, Hari P, Fraser R, et al. Autologous hematopoietic cell transplantation for multiple myeloma patients with renal insufficiency: a center for international blood and marrow transplant research analysis. *Bone Marrow Transplant.* 2017; 52:1616-1622.

9. Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple myeloma. *Lancet.* 2009; 374:324-339.

10. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood.* 2008; 111:2516-2520.

11. Bergin K, Moore E, McQuilten Z, et al. Design and development of the Australian and New Zealand (ANZ) myeloma and related diseases registry. *BMC Med. Res. Methodol.* 2016; 16:151-158.

12. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2005; 67:2089-2100.

13. Johnson DW, Jones GR, Mathew TH, et al. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations. *Med. J. Aust.* 2012; 197:224-225.

14. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* 2016; 17:e328-e346.

15. Australia and New Zealand Dialysis and Transplant Registry. The 40th Annual ANZDATA Report. Available at: http://www.anzdata.org.au; 2017. Accessed 30 March 2019.

16. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia.* 2014; 28:1122-1128.

17. Knudsen LM, Hippe E, Hjorth M, Holmberg E, Westin J. Renal function in newly diagnosed multiple myeloma--a demographic study of 1353 patients. The Nordic Myeloma Study Group. *Eur. J. Haematol.* 1994; 53:207-212.

18. Brenner H, Gondos A, Pulte D. Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010. *Haematologica.* 2009; 94:270-275.

19. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin. Proc.* 2003; 78:21-33.

20. Park S, Han B, Kim K, et al. Renal Insufficiency in newly-diagnosed multiple myeloma: analysis according to International Myeloma Working Group consensus statement. *Anticancer Res.* 2014; 34:4299-4306.

21. Nasr SH, Valeri AM, Sethi S, et al. Clinicopathologic correlations in multiple myeloma: a case series of 190 patients with kidney biopsies. *Am. J. Kidney Dis.* 2012; 59:786-794.

22. Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Bortezomib-based triplets are associated with a high probability of dialysis independence and rapid renal recovery in newly diagnosed myeloma patients with severe renal failure or those requiring dialysis. *Am. J. Hematol.* 2016; 91:499-502.

23. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. *J. Clin. Oncol.* 2005; 23:9219-9226.

24. Eleutherakis-Papaiakovou V, Bamias A, Gika D, et al. Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. *Leuk. Lymphoma.* 2007; 48:337-341.

25. Rayner HC, Haynes AP, Thompson JR, Russell N, Fletcher J. Perspectives in multiple myeloma: survival, prognostic factors and disease complications in a single centre between 1975 and 1988. *Q. J. Med.* 1991; 79:517-525.

26. Blade J, Fernandez-Llama P, Bosch F, et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. *Arch. Intern. Med.* 1998; 158:1889-1893.

27. Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. *Eur. J. Haematol.* 2000; 65:175-181.

28. Kastritis E, Anagnostopoulos A, Roussou M, et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. *Haematologica.* 2007; 92:546-549.

29. Kastritis E, Zervas K, Symeonidis A, et al. Improved survival of patients with multiple myeloma after the introduction of novel agents and the applicability of the International Staging System (ISS): an analysis of the Greek Myeloma Study Group (GMSG). *Leukemia.* 2009; 23:1152-1157.

30. Augeul-Meunier K, Chretien ML, Stoppa AM, et al. Extending autologous transplantation as first line therapy in multiple myeloma patients with severe renal impairment: a retrospective study by the SFGM-TC. *Bone Marrow Transplant.* 2018; 53:749-755.

Table 1. Patient characteristics at diagnosis (eGFR <60 versus eGFR ≥60 mL/min/1.73m^2)

	eGFR < 60	eGFR ≥ 60	P value
N	383	686	
Serum creatinine, µmol/L, median	143.0 (113.0, 229.0)	76.0 (67.0, 88.0)	<0.001
eGFR	39.0 (21.0, 51.0)	83.0 (71.0, 90.0)	<0.001
Paraprotein type			
IgG	202/379 (53.3%)	415/679 (61.1%)	
IgA	70/379 (18.5%)	142/679 (20.9%)	
IgM	2/379 (0.5%)	3/679 (0.4%)	
IgD	6/379 (1.6%)	3/679 (0.4%)	
Light chain Kappa	61/379 (16.1%)	68/679 (10.0%)	
Light chain Lambda	35/379 (9.2%)	31/679 (4.6%)	
Non-secretory MM	2/379 (0.5%)	12/679 (1.8%)	
Biclonal	1/379 (0.3%)	5/679 (0.7%)	
Light chain isotype			0.85
Kappa	173/275 (62.9%)	349/549 (63.6%)	
Lambda	102/275 (37.1%)	200/549 (36.4%)	
Age (years), median (IQR)	71.6 (63.2, 79.1)	64.5 (56.5, 71.0)	<0.001
Age > 70 years	212/383 (55.4%)	188/686 (27.4%)	<0.001
Gender (Male)	233/383 (60.8%)	421/685 (61.5%)	0.84
ISS = 3	191/289 (66.1%)	64/513 (12.5%)	<0.001
R-ISS = 3	62/181 (34.3%)	18/351 (5.1%)	<0.001
β2 microglobulin, median (IQR), mg/L	6.9 (4.6, 12.2)	3.0 (2.3, 4.1)	<0.001
Albumin, g/L	33 (28,37)	35 (31, 40)	<0.001
High-risk group (FISH or LDH)*	79/138 (57.2%)	126/284 (44.4%)	0.01
High-risk FISH †	50/160 (31.3%)	82/346 (23.7%)	0.07
LDH (U/L), median (IQR)‡	205.0 (164.0, 261.0)	186.0 (152.0, 234.0)	<0.001
LDH ≥ 300	32/234 (13.7%)	51/485 (10.5%)	0.21
ECOG performance status = 2-4	74/249 (29.7%)	84/467 (18.0%)	<0.001
Diabetes**	56/383 (14.6%)	62/686 (9.0%)	0.005
Moderate to severe cardiac disease	59/383 (15.4%)	57/686 (8.3%)	<0.001
Moderate to severe pulmonary disease	25/383 (6.5%)	31/686 (4.5%)	0.16
Abnormal liver function tests	10/383 (2.6%)	5/686 (0.7%)	0.01
Peripheral neuropathy	14/383 (3.7%)	14/686 (2.0%)	0.11
Hypercalcaemia	40/383 (10.4%)	30/686 (4.4%)	<0.001
Anaemia	163/383 (42.6%)	108/686 (15.7%)	<0.001
Bone lesions	202/383 (52.7%)	456/686 (66.5%)	<0.001

***High risk group= patients with high risk FISH (abnormalities: del17p, t(4;14), t(14;16), amp(1q21) or high LDH ≥300, †FISH abnormalities: del17p, t(4;14), t(14;16), amp1q21, ‡ Upper limit of normal for LDH=250 U/L, **diabetes requiring medication.**

Table 2. Treatment, response and survival (eGFR<60 versus eGFR≥60 mL/min/1.73 m^2)

	eGFR < 60	eGFR ≥ 60	P value
N	383	686	
Time from Dx to Rx (days), median (IQR)	15.0 (13.0, 18.0)	25.0 (22.0, 27.0)	<0.001
Time from Dx to ASCT (days), median (IQR)	199 (155-279)	195 (165-249)	0.55
Overall best clinical response (≥ PR*)	219/272 (80.5%)	457/547 (83.5%)	0.28
Bortezomib-based therapy	288/359 (80.2%)	568/648 (87.7%)	0.002
BCR in bortezomib-based therapy (≥ PR)‡	194/228 (85.1%)	423/492 (86.0%)	0.75
Thalidomide-based therapy	35/359 (9.7%)	54/648 (8.3%)	0.45
BCR in thalidomide-based therapy (≥ PR)	11/23 (47.8%)	31/46 (67.4%)	0.12
Lenalidomide-based therapy	11/359 (3.1%)	16/648 (2.5%)	0.58
BCR in lenalidomide-based therapy (≥ PR)	2/5 (40.0%)	7/9 (77.8%)	0.16
Carfilzomib-based therapy	8/359 (2.2%)	4/648 (0.5%)	0.02
BCR in carfilzomib-based therapy (≥ PR)	6/6 (100%)	1/1 (100%)	
Bortezomib or carfilzomib-based therapy	296/359 (82.5%)	571/648 (88.1%)	0.01
ASCT performed & age ≤ 70 years†	90/145 (62.1%)	335/429 (78.1%)	<0.001
ASCT conditioning			<0.001
Melphalan 200mg/m^2	70/97 (72.2%)	341/365 (93.4%)	
Melphalan 140mg/m^2	26/97 (26.8%)	17/365 (4.7%)	
Other**	1/97 (1.0%)	7/365 (1.9%)	
Plasma exchange therapy used	4/383 (1.0%)	12/686 (1.7%)	0.36
PFS (m), median (95% CI)	24.9 (21.3-28.5)	33.1 (29.7-36.4)	<0.001
Overall survival (m), median (95% CI)	47.2 (41.9-50.4)	67.1 (58.8+)	<0.001
Cause of death: disease-related (MM)	61/70 (87%)	69/81 (85%)	0.73
Deceased patients	119 (31.1%)	118 (17.2%)	
No. of chemotherapy regimens administered in deceased patients (median, IQR)	1.5 (1,3)	2 (1, 3)	0.08

All chemotherapy drug and response variables relate to first-line therapy, *≥PR= partial response or better to therapy, ‡BCR=best clinical response, †patients with diagnosis date ≥ 1 year prior to data extract and with follow-up data (age ≤ 70 is used as this is consensus practice for transplant eligibility in Australia and New Zealand and only ten patients aged >70 years had ASCT).

****Other=alternative doses of melphalan or other conditioning used.**

FIGURES – the figure title is above with the legend below if relevant

FIGURE 1. PATIENT FLOW CHART

MGUS=MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE, SMM=SMOULDERING MULTIPLE MYELOMA, PCL=PLASMA CELL LEUKAEMIA

FIGURE 2. PROGRESSION-FREE AND OVERALL SURVIVAL IN MULTIPLE MYELOMA BY RENAL FUNCTION AT DIAGNOSIS: A AND B COMPARE EGFR<60 VERSUS ≥60 ML/MIN; C AND D COMPARE EGFR CATEGORIES FOR CHRONIC KIDNEY DISEASE

FIGURE 3. PROGRESSION-FREE AND OVERALL SURVIVAL IN PATIENTS WITH MULTIPLE MYELOMA AND RENAL IMPAIRMENT (EGFR<60 ML/MIN) AT DIAGNOSIS, IN PATIENTS WHO HAD AND DID NOT HAVE AUTOLOGOUS STEM CELL TRANSPLANT

FIGURE 4. PROGRESSION-FREE AND OVERALL SURVIVAL IN PATIENTS WITH MULTIPLE MYELOMA WHO HAD AN AUTOLOGOUS STEM CELL TRANSPLANT, COMPARING PATIENTS WITH EGFR<60 VERSUS ≥60 ML/MIN AT DIAGNOSIS

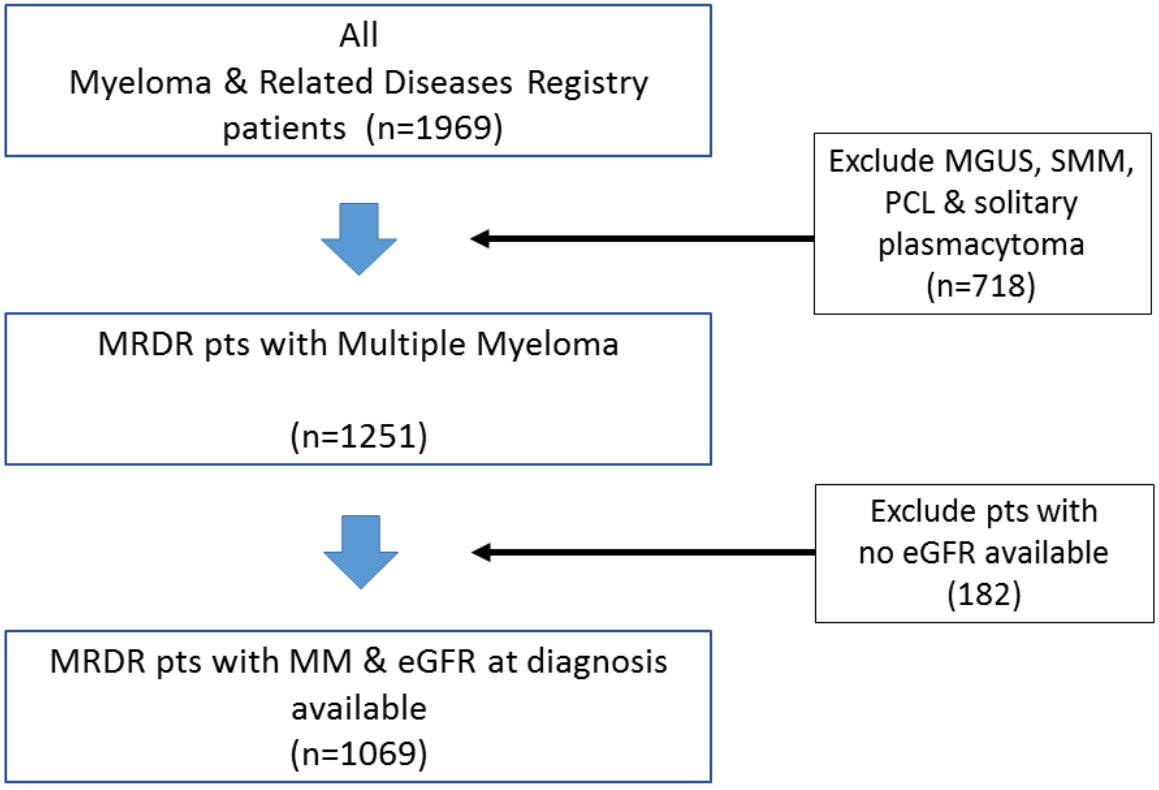
Supplementary Data

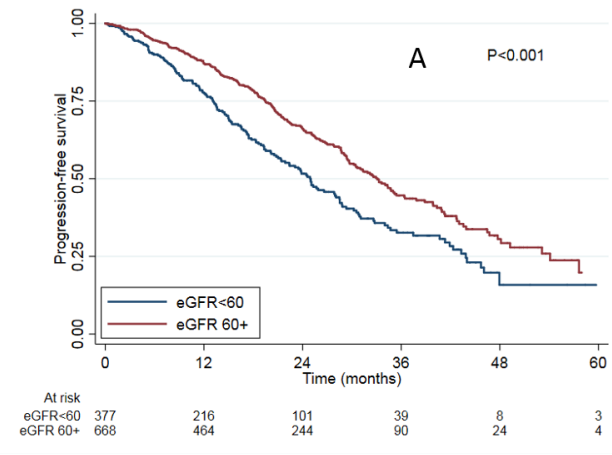
Table I

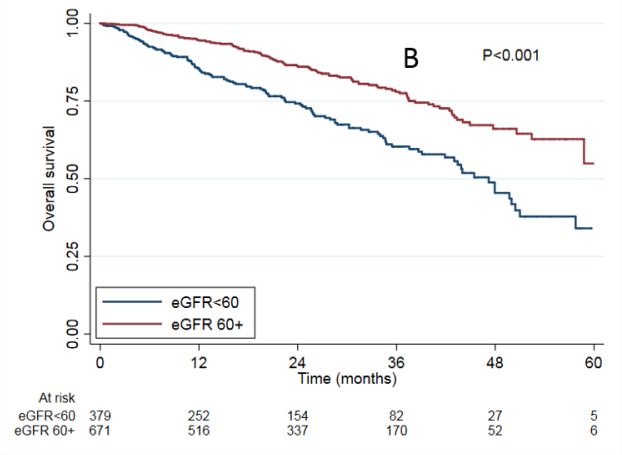
Characteristics of patients <70 years of age who were diagnosed with MM >1 year prior to data extraction and have follow up data (defined as TE in this study), according to ASCT versus No ASCT

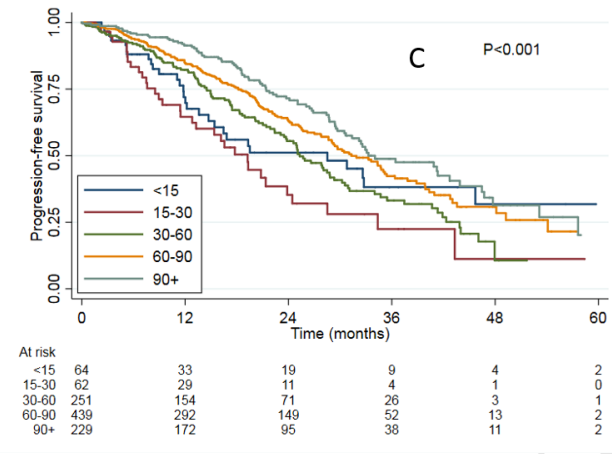
Factor	Level	No ASCT	ASCT	p-value
N		168	491	
Age at diagnosis, median (IQR)		65.0 (58.7, 68.1)	59.8 (53.0, 64.4)	<0.001
Gender (male)		100/168 (59.5%)	314/490 (64.1%)	0.29
ISS	1	26/110 (23.6%)	132/353 (37.4%)	0.029
	2	50/110 (45.5%)	131/353 (37.1%)	
	3	34/110 (30.9%)	90/353 (25.5%)	
R-ISS	1	4/80 (5.0%)	26/229 (11.4%)	0.12
	2	61/80 (76.3%)	175/229 (76.4%)	
	3	15/80 (18.8%)	28/229 (12.2%)	
ECOG Performance Status	0	36/109 (33.0%)	138/330 (41.8%)	<0.001
	1	42/109 (38.5%)	146/330 (44.2%)	
	2	19/109 (17.4%)	36/330 (10.9%)	
	3	8/109 (7.3%)	10/330 (3.0%)	
	4	4/109 (3.7%)	0/330 (0.0%)	
eGFR, median (IQR)		68 (45, 81)	81 (64, 90)	<0.001

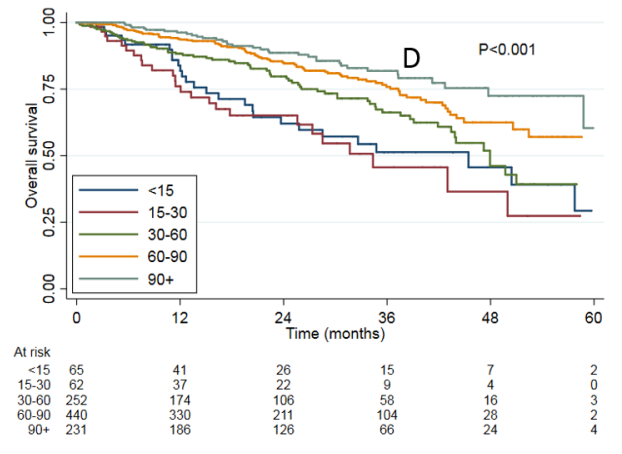
Although more complete data were available for ISS than R-ISS, and there appeared to be a significantly higher number of patients in lower ISS stages within the ASCT group, R-ISS is considered to be more informative given the greater reliance of ISS on beta-2 microglobulin (being one of 2 parameters) which can be affected by eGFR. The absence of a difference in R-ISS indicates no significant difference in MM stage in potential TE patients who received or did not receive an ASCT.

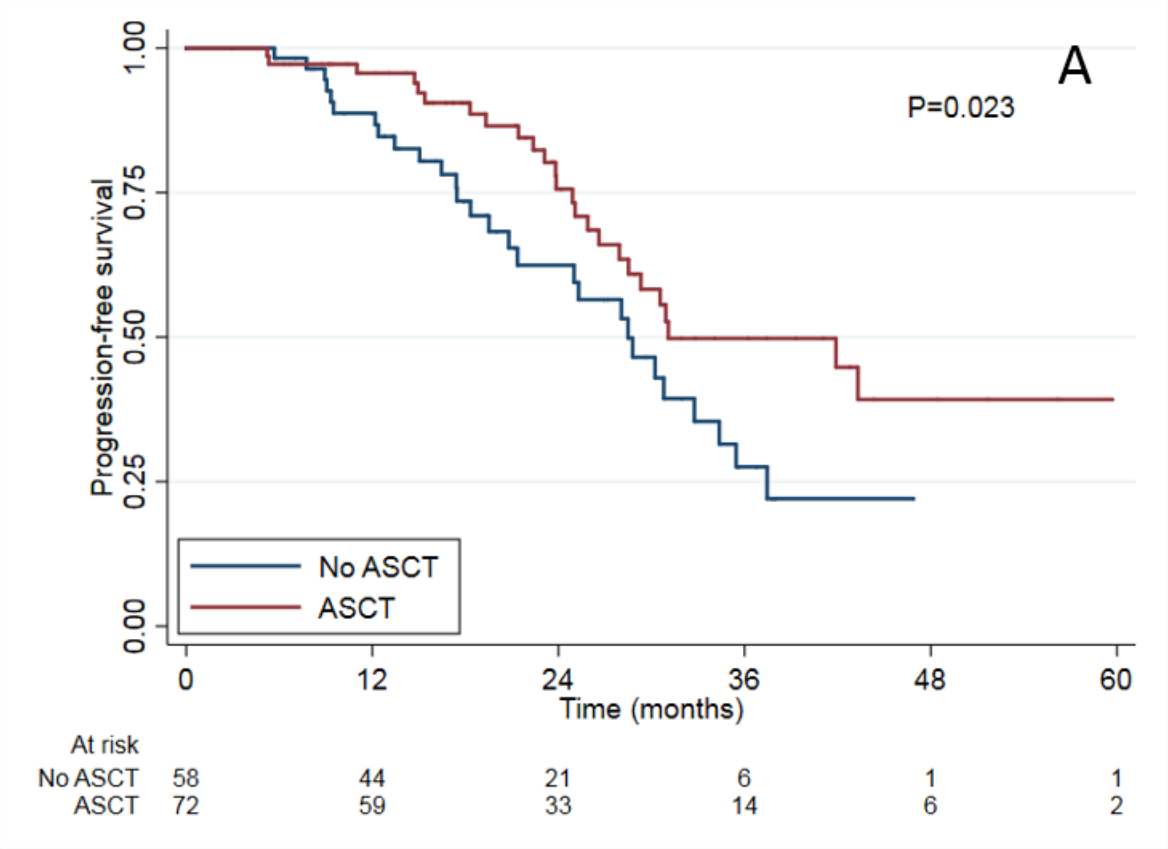

All
Myeloma & Related Diseases Registry patients (n=1969)
Exclude MGUS, SMM, PCL & solitary plasmacytoma (n=718)
MRDR pts with Multiple Myeloma
(n=1251)
Exclude pts with no eGFR available (182)
MRDR pts with MM & eGFR at diagnosis available
(n=1069)



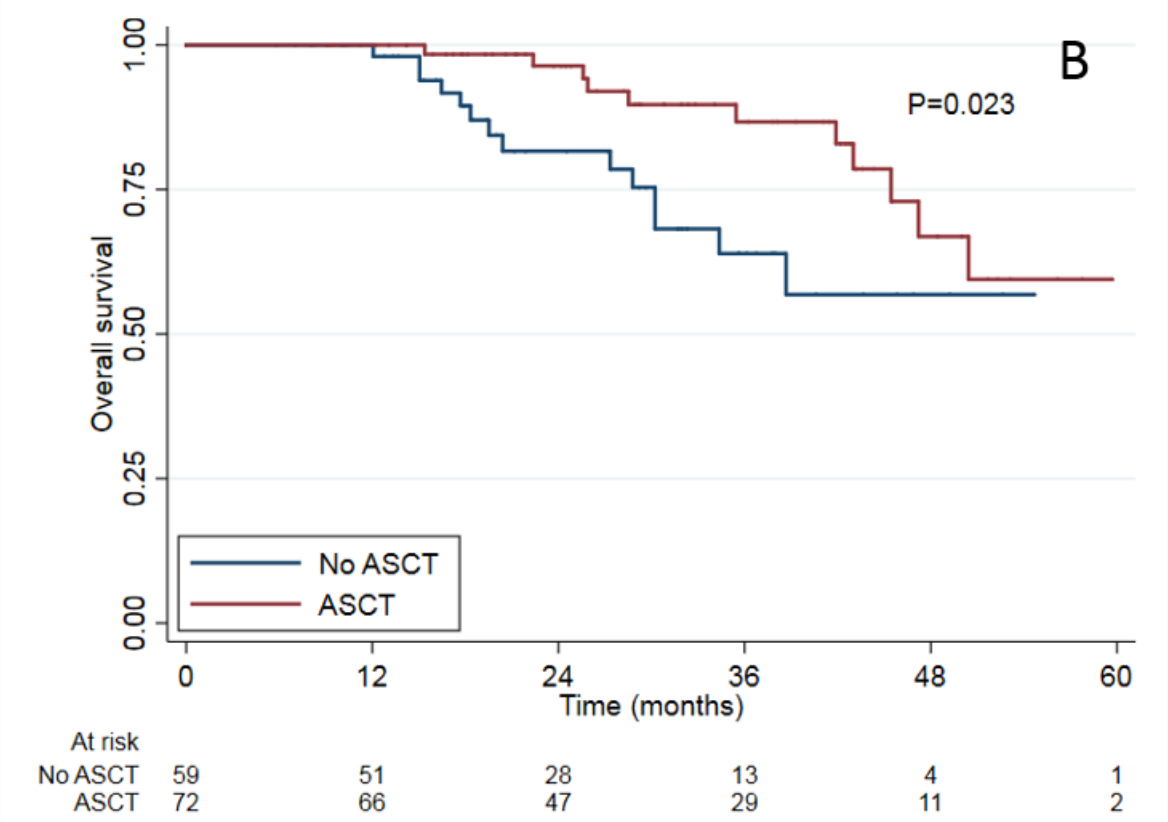




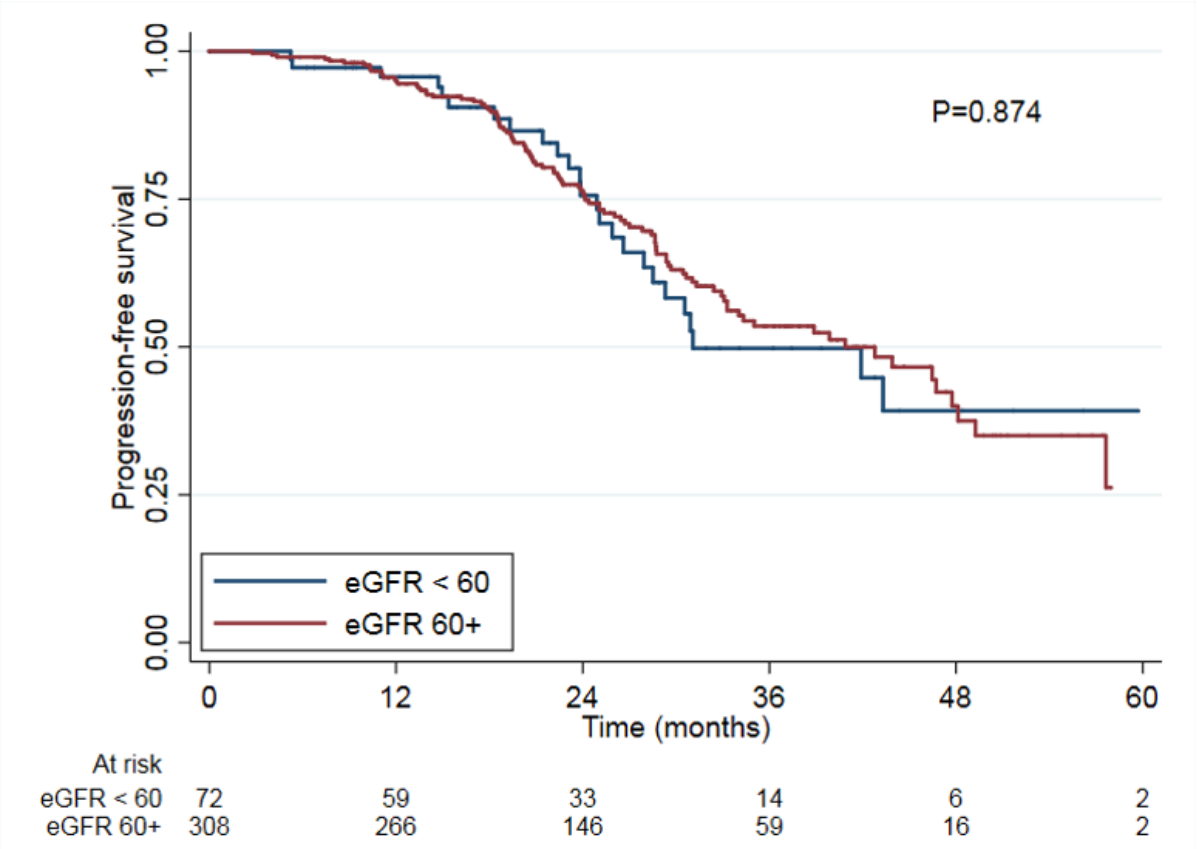




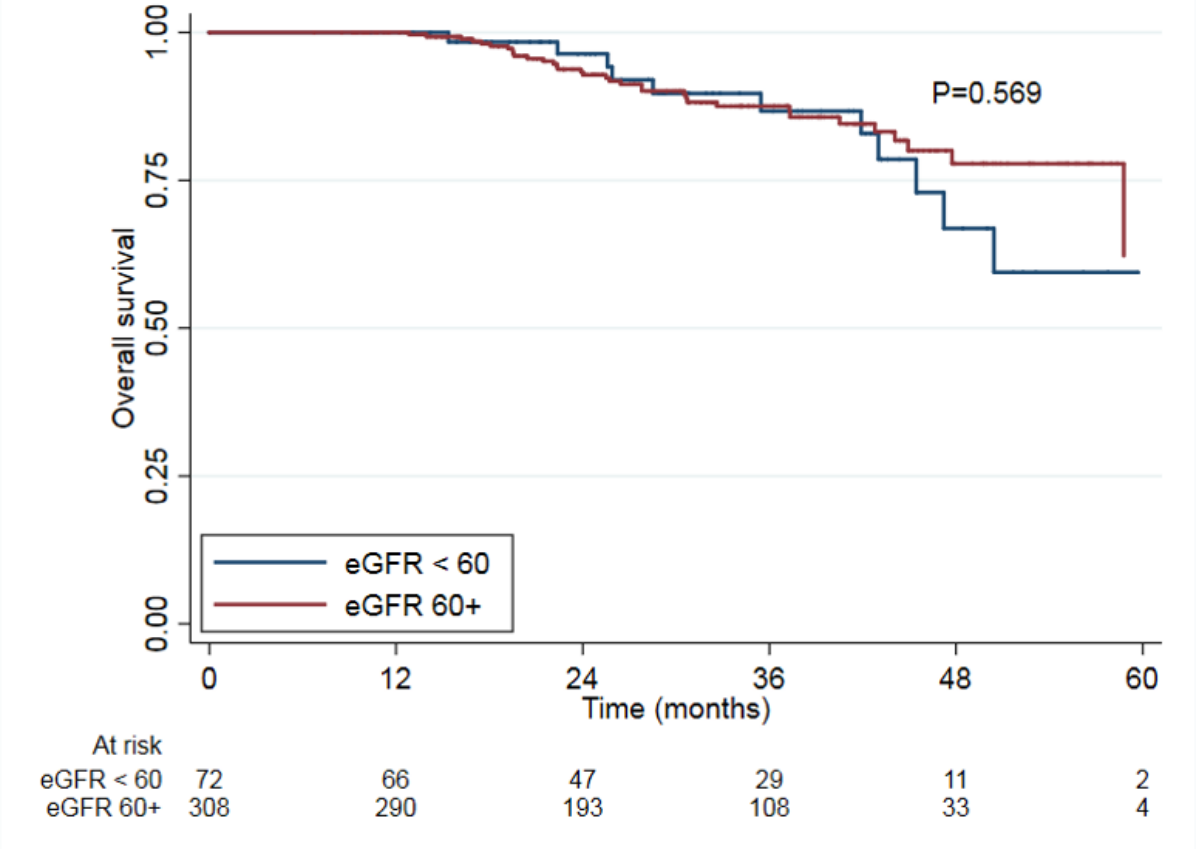
At risk						
No ASCT	58	44	21	6	1	1
ASCT	72	59	33	14	6	2



At risk						
No ASCT	59	51	28	13	4	1
ASCT	72	66	47	29	11	2



At risk						
eGFR < 60	72	59	33	14	6	2
eGFR 60+	308	266	146	59	16	2



At risk						
eGFR < 60	72	66	47	29	11	2
eGFR 60+	308	290	193	108	33	4