original reports

Response and Survival Estimates of Patients With Plasma Cell Myeloma in a Resource-Constrained Setting Using Protocols From High-Income Countries: A Single-Center Experience From Sri Lanka

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abstract

PURPOSE There is a significant disparity in global cancer care and outcome between countries. Progress in the treatment of symptomatic plasma cell myeloma (PCM) in high-income countries is not seen in low- and middle-income countries.

MATERIALS AND METHODS This is was a retrospective cohort study of all patients diagnosed with PCM between May 1, 2013, and September 30, 2021, at the first hemato-oncology center in Sri Lanka. We aimed to provide data on clinicopathologic characteristics, response, and survival estimates.

RESULTS A total of 79 patients with PCM received first-line therapy during the study period. The median age was 64 years, and approximately one third (33%) of patients were older than 70 years. There were 42 (53%) males and 37 females. Hypercalcemia, renal impairment, anemia, and bone disease were detected in 36.7%, 38%, 72.1%, and 81%, respectively. Thirty-nine, 34, and six patients received a combination of cyclophosphamide, thalidomide, and dexamethasone; bortezomib, thalidomide, and dexamethasone; and other treatments, respectively. The overall response rate (≥ partial response) was approximately 97% for both cyclophosphamide, thalidomide, and dexamethasone and bortezomib, thalidomide, and dexamethasone. Twenty-three (29%) of these patients died during the study period, but only 14 (18%) died due to PCM or associated sepsis. After a median follow-up of 40.6 months (range, 35.2-59.07 months), the median overall survival was 84.2 months (95% CI, 60.87 to not available). The 5-year estimated overall survival was 65%.

CONCLUSION To our knowledge, this is the only well-characterized study on long-term survival of patients with PCM in Sri Lanka. We have shown that it is possible to successfully apply Western treatment and supportive care protocols to the local population. These published data will help to benchmark and improve the treatment and develop blood cancer care in the local setting.

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INTRODUCTION

Although global cancer death rate has declined, there are socioeconomic inequalities and racial gap in cancer mortality. Poorer countries have a few folds higher mortality in some cancers compared with those of affluent countries.[1] However, data related to geographical differences and clinicopathologic and global survival variability are not well-documented, with a correlation between poverty and lack of accessibility to health care and vice versa in low-income countries.[2]

Plasma cell myeloma (PCM) is the second commonest hematologic malignancy, which accounts for 15%-20% of cases.[3] Incidence of PCM has increased over time, but the death rate has fallen because of improvement in polychemotherapy and radiotherapy.[4]

CONTEXT

Key Objective

Plasma cell myeloma (PCM) is a common type of blood cancer. The incidence of PCM has increased over time, but the death rate has fallen because of development of new treatment modalities and protocols. However, the availability of agents and applicability of protocols in low- and middle-income countries are debatable.

Knowledge Generated

To our knowledge, this is the only well-characterized study on long-term survival of patients with PCM in Sri Lanka. It provides data on response and long-term survival of patients with PCM treated with common treatment protocols used in high-income countries.

Relevance

These findings show the successful application of treatment and supportive care protocols from high-income countries in the setting of limited resources. These published data will help to benchmark and improve the treatment and develop blood cancer care in the local setting.

Sri Lanka is a developing country with a diverse health care structure with no dedicated hemato-oncology/clinical hematology centers and transplant facilities or access to novel anticancer agents at the time this study was started. There are no published data on characteristics or survival of PCM in Sri Lanka. We established the Lanka Hospital Blood Cancer Centre (LHBCC) in 2013 as a self-funded hospital in Colombo, Sri Lanka, in collaboration with colleagues in government-subsidized hospitals. Previously, we have published data related to acute myeloid leukemia and Hodgkin lymphoma.[5,6] In addition, LHBCC was used for training purposes of first set of hemato-oncology trainees from government-subsidized hospitals.

The aim of the study was to analyze patient and disease characteristics and evaluate response and survival parameters in patients with newly diagnosed PCM. In the absence of published local data, we used studies from other Asian countries and high-income countries for comparison.

MATERIALS AND METHODS

Treatment Site and Patients

LHBCC is a dedicated unit for treatment of hematologic malignancies with trained staff. Treatment and supportive care protocols from the United Kingdom[7] were used with 2 decades of experience of the first author at tertiary care centers in the United Kingdom. All nursing staff had yearly training on administration of chemotherapy and supportive care methods. Medical aspects of hemato-oncology services were provided by full-time British-trained clinical hematologists, visiting general oncologists, and other supportive care specialists.

All patients with a diagnosis of PCM who presented to the LHBCC and completed the first-line therapy between May 1, 2013, and September 30, 2021, were included in the analysis. The diagnosis was based on a WHO classification of hematologic malignancies.[8]

Clinical Management and Outcome Measurement

Patients were treated with combination chemotherapy after obtaining written informed consent with 28-day cycles of cyclophosphamide 500 mg once per week, thalidomide 50 mg once per day increased to 100 mg once per day if tolerated, dexamethasone 40 mg once per day on days 1-4 and 8-11 (cyclophosphamide, thalidomide, and dexamethasone [CTD]); or 28-day cycles of bortezomib 1.3 mg/m^2 once on days 1, 4, 8, and 11; thalidomide 50 mg once per day increased to 100 mg once per day if tolerated, and dexamethasone 40 mg once per day on days 1-4 and 8-11 (bortezomib, thalidomide, dexamethasone [BTD]). A maximum of four cycles if tolerated. In addition, all patients received acetylsalicylic acid 75 mg once per day as prophylaxis for deep venous thrombosis,[9] acyclovir 400 mg twice a day as antiviral prophylaxis, and zoledronic acid (4 mg once every 28 days) until progression International Myeloma Working Group uniform response and survival criteria were used for response assessment.[10]

Statistical Analysis

Response to therapy and the survival status at the last follow-up were recorded, and analyses were performed using various survival analysis techniques through RStudio (RStudio Team, 2020). The median length of follow-up was computed using the reverse Kaplan-Meier estimator.[11] Kruskal-Wallis test was used to compare median age, calcium level, creatinine, and hemoglobin (HgB) level at presentation among patients who underwent different treatments.[12] To evaluate the difference in survival between different groups, the log-rank test was used and various proportion comparisons among treatment groups were made using chi-square test for independence.[13] Verbal consent was taken from patients for storage and analysis of data, and written approval was granted by the Lanka Hospital ethical committee for analysis and publication of anonymized data.

Ethical Committee Approval

This study was considered as a quality-improvement activity, and approval was obtained from the Lanka Hospitals medical research and the ethics committee for the collection and analysis of anonymized data. Informed consent was obtained from all patients.

RESULTS

Demographic and Clinical Characteristics and Treatment

Demographic and clinical characteristics of patients with PCM who received first-line therapy in LHBCC are summarized in Table 1 and Figure 1. A total of 79 patients with PCM received first-line therapy during the study period. The median age was 64 years, and approximately one third (33%) of patients were older than 70 years. There were 42 (53%) males and 37 females; 36.7%, 38%, 72.1%, and 81% had hypercalcemia, renal impairment, anemia, and bone disease, respectively. Thirty-nine, 34, and six patients received a combination of CTD, BTD, and other treatments, respectively. Demographic and clinical characteristics of patients with PCM who received first-line therapy in LHBCC according to treatment type are summarized in Table 2.

Response and Survival

The overall response (OR) rate (≥ partial response) was approximately 97% for both CTD and BTD groups. Response to therapy of patients with PCM who received first-line therapy in LHBCC according to treatment type is summarized in Table 3. Twenty-three (29%) of these patients died during the study period, but only 14 (18%) died due to PCM or associated sepsis (Table 4). Cause of death in 14 (61%) patients was sepsis (five in BTD and seven in CTD group).

TABLE 1. Demographic and Clinical Characteristics of Patients With Plasma Cell Myeloma Who Received First-Line Therapy in Lanka Hospital Blood Cancer Center

Variable	Level	No. (%)
Age, median, years	64.0	79
Age, years	< 70	53 (67.1)
	≥ 70	26 (32.9)
Sex	Male	42 (53.2)
	Female	37 (46.8)
Hypercalcemia	Yes	27 (36.7)
	No	52 (63.3)
Renal impairment	Yes	30 (38.0)
	No	49 (62.0)
HgB, g/L	≥ 100	22 (27.9)
	< 100	57 (72.1)
Myeloma bone disease	Yes	64 (81.0)
	No	15 (19.0)
Treatment type	CTD	39 (49.4)
	BTD	34 (43.0)
	Other	6 (7.6)

Abbreviations: BTD, bortezomib, thalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; HgB, hemoglobin.

After a median follow-up of 40.63 months (95% CI, 35.2 to 59.07), the median overall survival (OS) was 84.2 months (95% CI, 60.87 to not available) and the estimated 5-year OS was 65%. The median OS for the CTD group was 84.2 (95% CI, 60.9 to not available; restricted mean [SE] of OS 69.88 [5.29]), and the median OS for the BTD group was not reached (restricted mean [SE] of OS 49.9 [3.4]), as illustrated in Table 5 and Figure 2.

According to the log-rank test, there was no significant difference in OS according to age, sex, hypercalcemia, renal impairment, anemia, or bone disease at presentation (Table 5 and Fig 2). In addition, there was no significant difference in survival curves between the two treatment groups (Table 5 and Fig 3A) or according to depth of response (achieving complete response [CR], VGPR, or partial response; Table 5, Fig 3B).

Safety

Two patients (2.5%) in our study had deep venous thrombosis while on treatment and aspirin prophylaxis. Seventy-two (98.6%) patients in this group treated with CTD and bortezomib, thalidomide, and dexamethasone completed intended four cycles of therapy. Only one patient discontinued treatment because of grade 3 peripheral neuropathy.

Twenty-three (29%) patients died during the study period, but only 14 (18%) died due to PCM or associated sepsis. Seven patients (9%) died within one year of diagnosis.

DISCUSSION

Curing most blood cancers is challenging in low-income countries, especially in a country without free and easy access to the specialty of blood cancer care, transplant facilities, or newer treatment options. Studies from low-income countries comparing clinicopathologic features and survival parameters with data from high-income countries have shown early-onset and late-stage presentation with reduced survival.[14] There is a paucity of trained clinical hematologists, hematopathologists, proper patient referral system, facilities for immunohistochemistry, and centralized review process in low- and middle-income countries.

Incidence of PCM varies among countries but has increased over the past few decades. The largest increase is in low- and middle-income countries.[15] It is known that African American populations show higher incidence, whereas Asian populations show lower incidence of PCM compared with White populations.[16-18] Waxman et al[19] showed higher incidence and younger age of onset in African Americans. Accurate and up-to-date cancer incidence data are required for health planning and to afford effective medication for every patient and to understand the underlying etiological

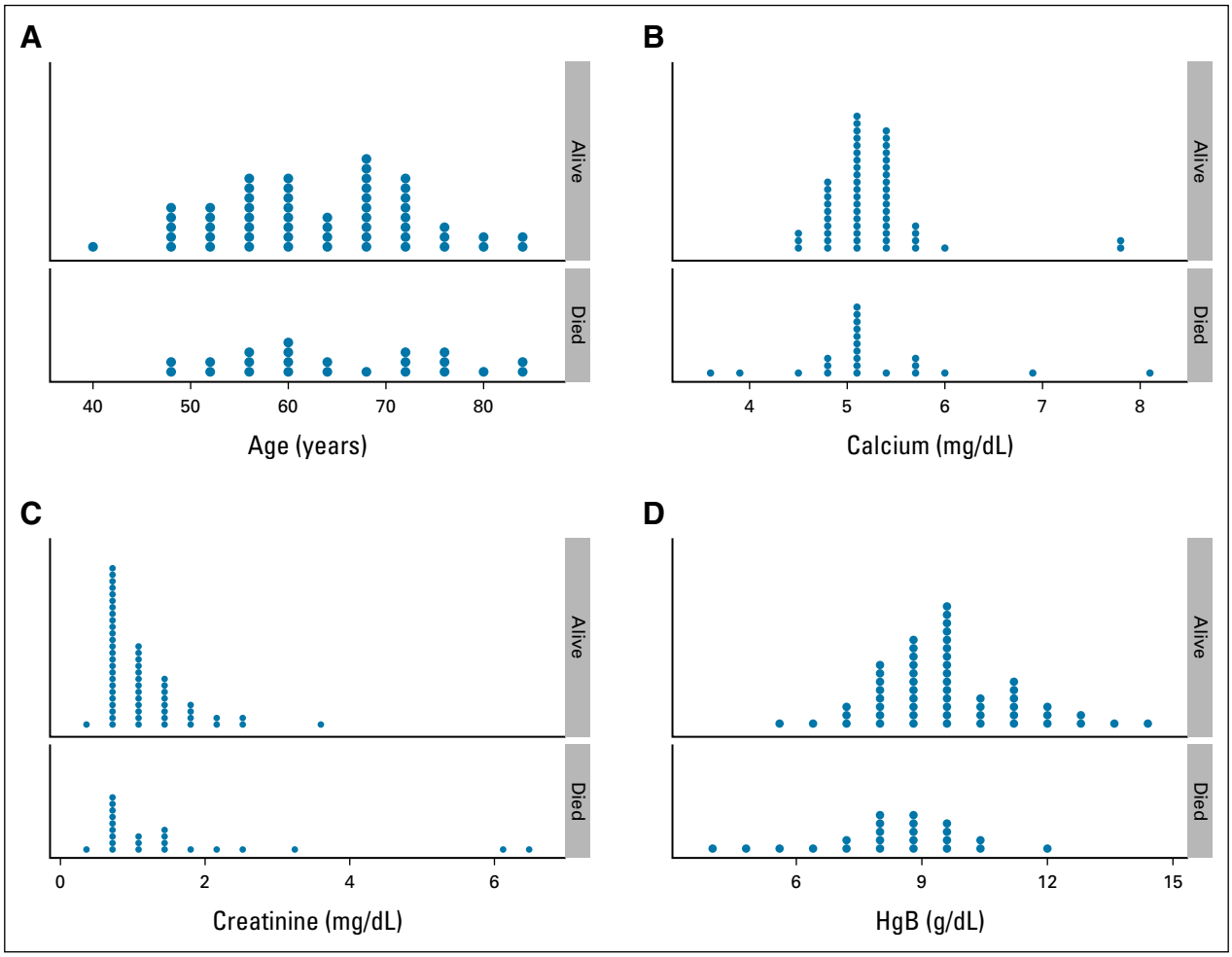

FIG 1. (A) Age, (B) serum calcium, (C) serum creatinine, and (D) HgB of patients with plasma cell myeloma treated in Lanka Hospital Blood Cancer Center. HgB, hemoglobin.

factors for the heterogeneity of PCM incidence.[15] Cowan et al[15] reported age-standardized incidence rate per 100,000 of 0.4-0.9 in Sri Lanka in the Global Burden of Multiple Myeloma study. There is a paucity of up-to-date statistics related to the incidence of PCM in Sri Lanka.

TABLE 2. Demographic and Clinical Characteristics of Patients With Plasma Cell Myeloma Who Received First-Line Therapy in Lanka Hospital Blood Cancer Center According to Treatment Type

Characteristic	CTD	BTD	Other	*P*
No. (%)	39 (49)	34 (43)	6 (8)	—
Sex (% male)	14 (36)	23 (68)	5 (83)	.008
Age, median, years	64.50	64.00	59.00	.993
Ca(I), median	5.24	5.16	5.20	.910
Cr, median	1.06	0.90	1.14	.197
HgB, median	9.20	9.25	8.45	.513
Bone disease, %	33 (85)	26 (76)	5 (83)	.668

Abbreviations: BTD, bortezomib, thalidomide, and dexamethasone; Ca(I), ionized calcium; Cr, creatinine; CTD, cyclophosphamide, thalidomide, and dexamethasone; HgB, hemoglobin.

The median age of incidence of PCM in White people is in the seventh decade according to previously published data.[16,20,21] However, it has been shown that the median age of onset in African Americans was at least a decade younger.[4,19] The median age at presentation in our cohort was 64 years, and more than two third are younger than 70 years. However, the median age of onset in our study is

TABLE 3. Percentage (%) Response of Patients With Plasma Cell Myeloma Who Received First-Line Therapy in Lanka Hospital Blood Cancer Center According to Treatment Type

Response	CTD	BTD	Other Treatment
CR	15	15	—
VGPR	41	47	83
PR	41	35	17
SD	3	3	—

Abbreviations: BTD, bortezomib, thalidomide, and dexamethasone; CR, complete response; CTD, cyclophosphamide, thalidomide, and dexamethasone; PR, partial response; SD, stable disease; VGPR, very good partial response.

TABLE 4. Number of Events (and censored) of Patients With Plasma Cell Myeloma Who Received First-Line Therapy in Lanka Hospital Blood Cancer Center According to Treatment Type

Therapy	Total No.	No. of Events (deaths)	Censored
CTD	34	5	29
BTD	39	15	24
Others	6	3	3
Overall	79	23	56

Abbreviations: BTD, bortezomib, thalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone.

higher than that reported by some Asian studies. An Iranian study has shown the median age of presentation to be 51 years,[22] and a Pakistani study has shown it to be 57 years.[20] In another study from Vasquez et al[23] from a middle-income country, the median age was 56 years and 59% were male. However, our data are similar to the data of an Asian Myeloma Network study, in which the median age of presentation was 62 years.[24] Larger and more extensive research studies may be needed to clarify the disparity in median age of presentation in PCM in middle- and low-income countries.

Our cohort has shown a slight male predominance (53.2%), which is in keeping with some other published data.[24,25] However, Sultan et al[20] reported a higher percentage (70%) of affected males in their study.

In an Asian study, the majority of patients presented with symptomatic anemia and backache (80%).[20] In our cohort, 81% presented with myeloma bone disease and 72% had a HgB of < 100 g/L. Although there is no information related to the cause of backache in the study by Sultan et al, it is likely they suffered from myeloma bone disease. These figures are significantly higher than those reported in trials from high-income countries.[26] The study by Rosiñol et al had only 32% of patients with HgB of < 100 g/L. It is likely less symptomatic patients present for treatment in high-income countries and with more symptomatic disease in low-income countries. This may be due to lack of knowledge related to early signs of cancer and proper infrastructure for early cancer detection as in high-income countries.

Conventional treatments for PCM include chemotherapy and radiation therapy. Addition of immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), and monoclonal antibodies (daratumumab, isatuximab, and elotuzumab) significantly improved the survival of patients with PCM.[27,28] Induction followed by high-dose therapy and lenalidomide maintenance is recommended as standard of care in certain settings in high-income countries.[29-31]

Large international clinical trials from high-income countries have set the stage for evidence-based guidelines for treatment of PCM, but heterogeneous care of patients in low-income countries results in inferior outcomes.[32] However, access to effective care is limited in many low- and middle-income countries, causing huge disparity in cancer care.[15]

In our study, 39 patients (49%) received CTD and 34 (43%) received BTD. In another Asian study by Hameed et al[22] in 2017, most of the patients (n = 59; 71.9%) were treated with the CTD regimen and 13 (15.8%) received bortezomib-based treatment. Our study showed a higher percentage of patients receiving bortezomib-based treatment probably as the study by Hameed et al, was from July 2012 to December 2015 and our study was from 2013 to 2021. Thalidomide was used as first-line therapy in 2013 in LHBCC, considering the efficacy of it in high-income countries.[33,34] Lenalidomide and bortezomib were approved in Asia in 2016.[15] We started using bortezomib in 2016 at the LHBCC. This explains a shorter follow-up in the BTD group. There is a long delay in new cancer medications reaching patients in low-income countries, causing unfavorable outcome.

A study by Vasquez et al[23] from a middle-income country showed a total response rate of 69.5% using CTD. Our study showed 15.3% CR rate and 97% OR rate in the group treated with CTD, which is higher than that reported by the study by Vasquez et al. The finding in our study is comparable with the results reported in the myeloma IX trial by Morgan et al.[7] The OR rate and CR rate with CTD in their study were 82.5% and 13.0%, respectively.[7] Although our study has a smaller number of patients, this showed better response rates compared with publications from other middle-income countries and comparable results with those of high-income countries.

The cohort of patients treated with BTD in our study showed an OR rate of 97% and a CR rate of 14.7%. Moreau et al had shown similar results in a high-income setting. In their study, after four cycles of treatment, the OR rate was 92.3% and the CR rate was 13% in the BTD arm.[35] In a study by Cavo et al,[36] CR or near-complete response was 31% in the group receiving BTD in a high-income setting. An Italian study by Rosiñol et al[26] reported a CR rate of 35%, but the study showed only 14.7% of CR. We had less number of patients with CR, probably because of not performing bone marrow assessment to define CR. They were classified into groups of lesser response.

The 5-year survival rate in PCM has improved significantly over the past few decades. However, only 10%-20% of patients achieved expected survival compared with matched general population.[37] There is a wide variation in reported survival parameters in different studies. Immunomodulatory drugs and proteasome inhibitors were shown to affect OS when used as first-line therapy.[24] The majority of patients in our study received these drugs and showed a median OS of 84.2 months and an estimated 5-year survival rate of 65%. To our knowledge, this is the only available Sri Lankan study with a long-term follow-up of patients up to a median follow-up of nearly 4 years.

TABLE 5. Median Overall Survival (95% CI), Restricted Mean, and Five-Year Survival Rate of Patients With Plasma Cell Myeloma Who Received First-Line Therapy in Lanka Hospital Blood Cancer Center According to Clinical Parameters and Treatment Type

Parameter	All	CTD	BTD
Median OS	84.20 (60.87 to NA)	84.20 (60.87 to NA)	Not reached (NA to NA)
Restricted mean	68.09 (4.52)	69.88 (5.29)	49.9 (3.4)
5-year survival rate	0.651	0.667	0.818[a]
Log-rank *P*			.2
Age, years			
< 70			
Median OS	Not reached (60.9 to NA)	Not reached (60.9 to NA)	Not reached (NA to NA)
Restricted mean	72.0 (5.26)	74.6 (5.94)	50.2 (4.24)
≥ 70			
Median	75.1 (41.2 to NA)	75.1 (35.5 to NA)	Not reached (NA to NA)
Restricted mean	58.6 (6.76)	58.0 (9.03)	49.8 (5.48)
Log-rank *P*	.2	.1	.9
Sex			
Male			
Median	75.1 (53.1 to NA)	Not reached (75.1 to NA)	Not reached (NA to NA)
Restricted mean	66.3 (6.75)	77.3 (8.02)	45.6 (4.92)
Female			
Median	84.2 (60.9 to NA)	84.2 (39.6 to NA)	Not reached (NA to NA)
Restricted mean	70.3 (5.93)	65.2 (6.80)	58.2 (0.00)
Log-rank *P*	.6	.3	.09[b]
Hypercalcemia			
Yes			
Median	Not reached (60.9 to NA)	Not reached (NA to NA)	Not reached (27.4 to NA)
Restricted mean	73.7 (6.98)	84.4 (5.80)	46.8 (7.13)
No			
Median	84.2 (53.1 to NA)	75.1 (39.6 to NA)	Not reached (NA to NA)
Restricted mean	65.6 (5.71)	62.3 (7.07)	50.7 (4.05)
Log-rank *P*	.4	.07[b]	.8
Renal impairment			
Yes			
Median	60.9 (41.2 to NA)	84.2 (53.1 to NA)	Not reached (27.4 to NA)
Restricted mean	62.3 (7.55)	72.3 (8.04)	45.4 (6.49)
No			
Median	Not reached (75.1 to NA)	Not reached (55.2 to NA)	Not reached (NA to NA)
Restricted mean	71.5 (5.55)	69.4 (6.71)	52.8 (3.63)
Log-rank *P*	.4	1.0	.3
HgB, g/L			
< 100			
Median	75.1 (53.1 to NA)	75.1 (53.1 to NA)	Not reached (NA to NA)
Restricted mean	64.5 (5.23)	65.2 (6.19)	48.4 (4.43); Not reached (NA to NA)
≥ 100			
Median	Not reached (NA to NA)	Not reached (NA to NA)	Not reached (NA to NA)
Restricted mean	81.2 (7.73)	87.7 (7.52)	53.3 (4.68)
Log-rank *P*	.2	.1	.5

(Continued on following page)

TABLE 5. Median Overall Survival (95% CI), Restricted Mean, and Five-Year Survival Rate of Patients With Plasma Cell Myeloma Who Received First-Line Therapy in Lanka Hospital Blood Cancer Center According to Clinical Parameters and Treatment Type (Continued)

Parameter	All	CTD	BTD
Bone disease			
Yes			
Median	75.1 (55.2 to NA)	75.1 (55.2 to NA)	Not reached (NA to NA)
Restricted mean	62.6 (5.09)	64.8 (5.80)	49.3 (4.08)
No			
Median	Not reached (NA to NA)	Not reached (NA to NA)	Not reached (NA to NA)
Restricted mean	84.2 (7.55)	84.3 (10.40)	52.1 (5.70)
Log-rank *P*	.08[b]	.1	.8
Response			
CR			
Median	Not reached (75.1 to NA)	Not reached (75.1 to NA)	Not reached (NA to NA)
Restricted mean	81.3 (8.61)	78.8 (10.32)	58.2 (0.00)
VGPR			
Median	60.9 (53.1 to NA)	60.9 (39.6 to NA)	Not reached (NA to NA)
Restricted mean	58.9 (5.88)	59.8 (7.16)	51.5 (4.48)
PR			
Median	Not reached (55.2 to NA)	Not reached (NA to NA)	Not reached (27.4 to NA)
Restricted mean	71.6 (7.14)	76.9 (8.23)	45.4 (6.38)
SD			
Median	27.4 (NA to NA)	27.4 (NA to NA)	Not reached (NA to NA)
Restricted mean	27.4 (0.00)	27.4 (0.00)	58.2 (0.00)

NOTE. Log-rank *P* values for comparison of survival curves between different demographic and clinical parameters of all (79), CTD, and BTD treatment groups.

Abbreviations: BTD, bortezomib, thalidomide, and dexamethasone; CR, complete response; CTD, cyclophosphamide, thalidomide, and dexamethasone; HgB, hemoglobin; NA, not available; OS, overall survival; PR, partial response; SD, stable disease; VGPR, very good partial response.

[a]On the basis of the estimated survival rate at 58.2 months.

[b]Significant at .1.

Several Asian studies tried to assess the survival of patients with PCM. In an Iranian study performed from 2012 to 2015, the median OS was 48 months.[22] However, this study had a lower number of patients receiving bortezomib-based therapy. A study by Lu et al[21] reported an OS of 54 months and another study by Asian Myeloma Network (in which Sri Lanka is not a part of) reported an OS of 47 months.[24]

According to a study by Chan and Milne,[38] the median OS was 50.7 months in a population from New Zealand.[38] This study was conducted from 2012 to 2017 after the availability of novel myeloma agents. The OS reported in our study is significantly better than that in the aforementioned studies. Patients treated at LHBCC showed better survival compared with other studies from middle- and low-income countries. However, Vasquez et al reported a median OS of 81 months and a 5-year OS rate of 57.5% in a study from a middle-income country.[23]

Furthermore, we did not see a survival difference between patients treated with CTD and BTD. Similar results were reported by Rosiñol et al. The estimated OS rate at 4 years was 74% for patients treated with BTD, and there was no OS difference between BTD and other treatments groups.[26] Similarly, there was no significant OS difference in the CTD and BTD groups in a study published by Hameed et al.[22] Our data have a shorter follow-up in the BTD group compared with CTD because of late availability of bortezomib in Sri Lanka.

It has been shown that there are several disparities in PCM care depending on access to quality medical care and newer antimyeloma drugs.[32] There is a significant heterogeneity between different hospitals with regard to diagnostic and treatment facilities and access to trained personnel and supportive care in Sri Lanka. Superior results in our study may be due to selection bias. Patients treated at LHBCC, established in a self-funding hospital, may attract patients belonging to a higher socioeconomic and education level. Xu et al[39] have previously shown that high education levels may independently predict better survival outcome in patients with PCM in an Asian study. Furthermore, socioeconomic status is a global prognostic factor in PCM survival.[40] However, we recognize these

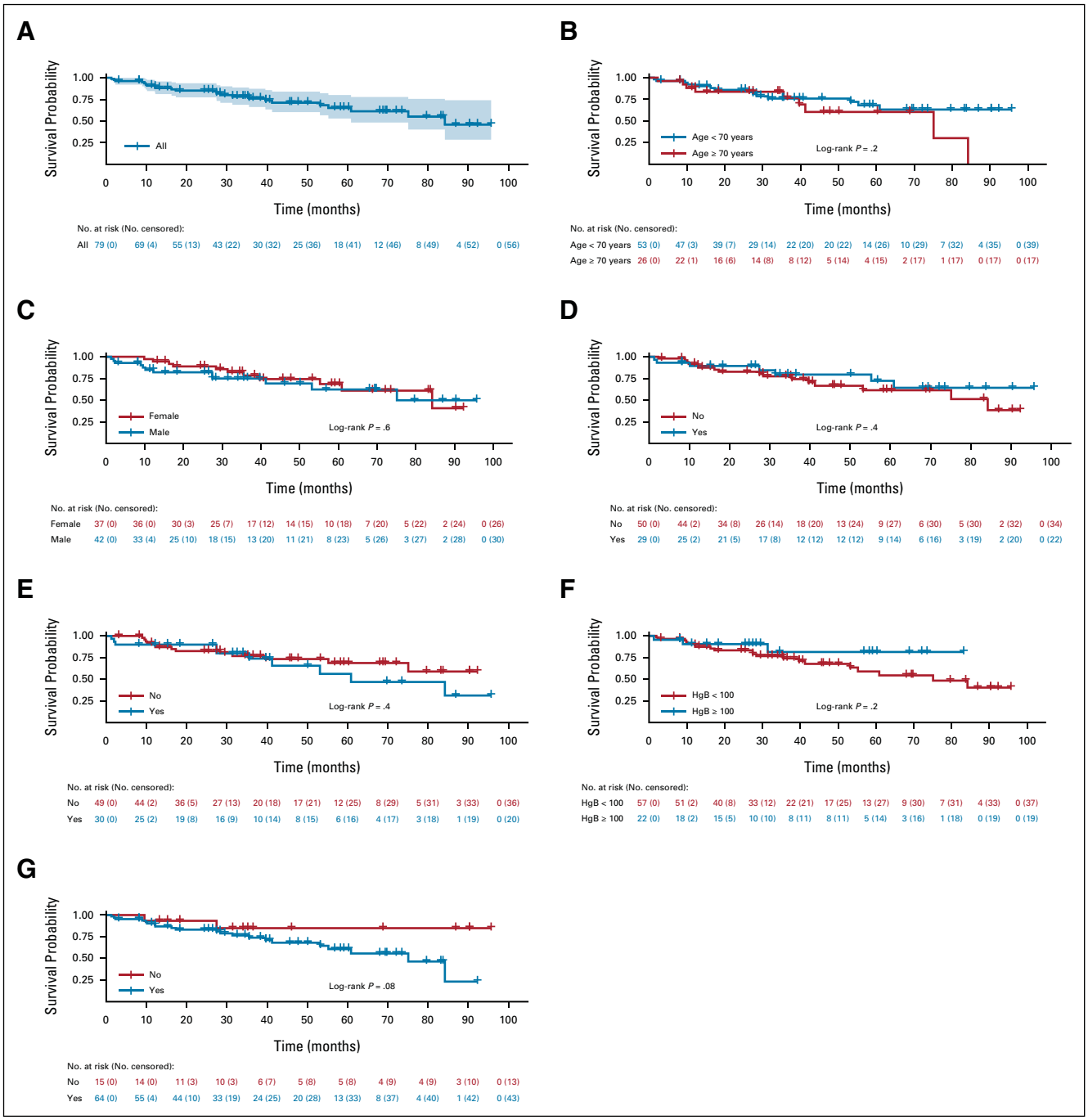

FIG 2. Kaplan-Meier survival curves of (A) patients with plasma cell myeloma who received first-line therapy in Lanka Hospital Blood Cancer Center and subanalysis according to (B) age, (C) sex, (D) hypercalcemia, (E) renal impairment, (F) anemia, and (G) bone involvement. HgB, hemoglobin.

results may not represent the survival of patients with PCM in Sri Lanka, and larger studies covering government-subsidized centers are needed for better evaluation.

Risk of thrombosis (VTE) is increased by 28-fold in patients with hematologic malignancies compared with 7- to 10-fold in patients with other cancers.[41] VTE thromboprophylaxis is recommended according to risk assessment: aspirin for low-risk patients and low-molecular-weight heparin for high-risk patients.[9] In a study from South America, the incidence of VTE was 6.8%.[23] However, there are no guidelines or publications related to VTE risk in Asian people, and maintenance of low-molecular-weight heparin is relatively expensive in the local setting. Furthermore, aspirin has been used in primary and secondary thromboprophylaxis.[42] This prompted us to the use of cheap alternative (aspirin) as VTE thromboprophylaxis. Further studies are needed to understand the best thromboprophylaxis policy for the local population.

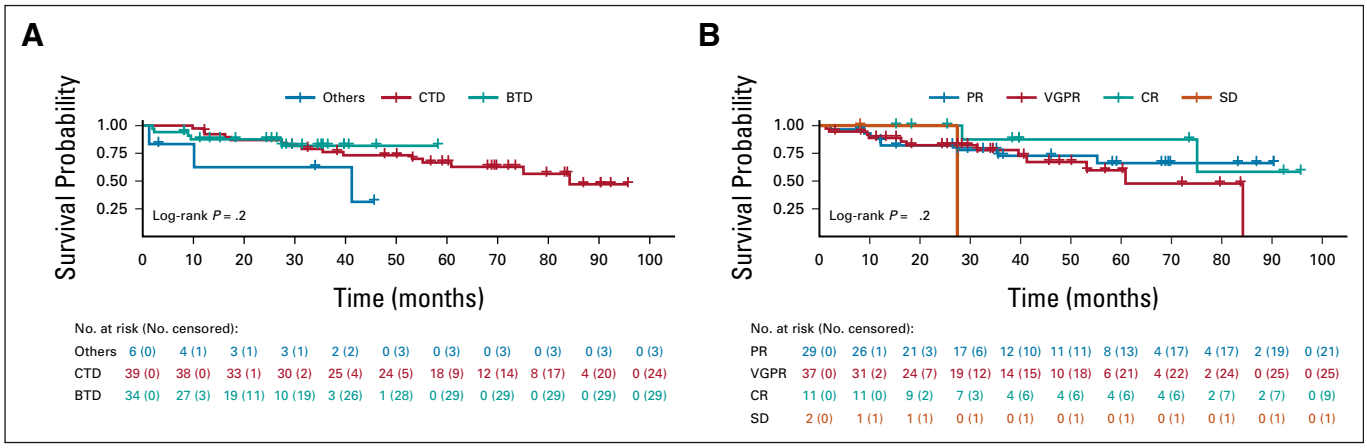

FIG 3. Kaplan-Meier survival curves of patients with plasma cell myeloma who received first-line therapy in Lanka Hospital Blood Cancer Center according to (A) treatment type and (B) response. BTD, bortezomib, thalidomide, and dexamethasone; CR, complete response; CTD, cyclophosphamide, thalidomide, and dexamethasone; PR, partial response; SD, stable disease; VGPR, very good partial response.

Twenty-three patients died during the study: fifteen in the CTD, five in the BTD, and three in the other treatment group. Cause of death in 14 (61%) patients was sepsis (five in BTD and seven in CTD group). More patients died in the CTD group because of other causes, and it may be due to longer follow-up and the age range was 48-86 years. Nine percent of patients died within one year of diagnosis in our study (three in the BTD, two in CTD, and two in other treatment). Three of those patients were older than 70 years. The early mortality is exclusively related to sepsis. We used a similar type of antimicrobial prophylaxis. Cause of death may be multifactorial, but the numbers are too small to draw conclusions. In a study by Kumar et al,[43] 13% of patients died during the first year, with age older than 70 years as a risk factor for early mortality. Although the number of patients in our study is too small to arrive at conclusions, it is likely sepsis is a major cause of mortality and further studies/interventions are needed to mitigate it.

We acknowledge that a limitation of this study was the small sample size, which may be due to selection bias toward better outcome. There were also no facilities for genetic risk classification and stem-cell transplants, and there were limitations on the available supportive care, including antibiotics, in Sri Lanka. In addition, it is not possible to compare with other general oncology centers or generalize these findings to the entire country. A larger study may be needed in the future with development of the specialty of blood cancer care in Sri Lanka.

To our knowledge, this is the only documented study related to outcome and applicability of Western treatment and supportive care protocols to Sri Lankan patients with PCM. We have previously shown that blood cancer care can be continued safely with higher success even during these testing times.[44] In this study, we have presented data to support the feasibility of establishing a successful and dedicated hemato-oncology/clinical hematology unit where not only patients were treated according to Western protocols but also participated in subspecialty training for hemato-oncology trainees from government-subsidized hospitals. These real-world data identify areas that need further attention and stress the importance of right treatment on the first presentation to improve outcome. We believe that these published data will help to benchmark and develop the specialty of blood cancer care in the local setting.

In conclusion, to our knowledge, this is the only well-characterized study on long-term survival of patients with PCM in Sri Lanka. We have shown that it is possible to successfully apply Western treatment and supportive care protocols to the local population. These published data will help to benchmark and improve the treatment and develop blood cancer care in the local setting.

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DATA SHARING STATEMENT

Data used in this study are available from the corresponding authors upon reasonable request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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REFERENCES

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69:7-34, 2019
2. Biasoli I, Castro N, Delamain M, et al: Lower socioeconomic status is independently associated with shorter survival in Hodgkin Lymphoma patients—An analysis from the Brazilian Hodgkin Lymphoma Registry. Int J Cancer 142:883-890, 2018
3. Ferlay J, Soerjomataram I, Dikshit R, et al: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136:E359-E386, 2015
4. Costa LJ, Brill IK, Omel J, et al: Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv 1:282-287, 2017
5. Hewamana S, Kandabadage L, Skandarajah T, et al: Applicability of protocols from high-income countries in a resource limited setting; real world data of histopathology, clinical features and long-term outcome of Hodgkin Lymphoma in Sri Lanka. EClinicalMedicine 38:100998, 2021
6. Hewamana S, Kandabadage L, Skandarajah T, et al: Applicability of Western protocols in resource-limited setting: Real-world data of long-term outcome of intensive treatment of adult acute myeloid leukaemia in Sri Lanka. eJHaem 2, 2021
7. Morgan GJ, Davies FE, Gregory WM, et al: Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood 118:1231-1238, 2011
8. World Health Organization: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised ed 4). Lyon, France, International Agency for Research on Cancer, 2017
9. Palumbo A, Rajkumar SV, Dimopoulos MA, et al: Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 22:414-423, 2008
10. Durie BGM, Harousseau J-L, Miguel JS, et al: International uniform response criteria for multiple myeloma. Leukemia 20:1467-1473, 2006
11. Clark TG, Altman DG, Stavola BLD: Quantification of the completeness of follow-up. Lancet 359:1309-1310, 2002
12. Kruskal WH, Wallis WA: Use of ranks in one-criterion variance analysis. J Am Stat Assoc 47:583-621, 1952
13. Agresti A, Kateri M: Categorical Data Analysis. Berlin, Germany, Springer, 2011, pp 206-208
14. Acquah ME, Hsing AW, McGuire V, et al: Presentation and survival of multiple myeloma patients in Ghana: A review of 9 cases. Ghana Med J 53:52-58, 2019
15. Cowan AJ, Allen C, Barac A, et al: Global burden of multiple myeloma: A systematic analysis for the global burden of disease study 2016. JAMA Oncol 4:1221-1227, 2018
16. Dispenzieri A, Kyle RA: Multiple myeloma: Clinical features and indications for therapy. Best Pract Res Clin Haematol 18:553-568, 2005
17. Landgren O, Weiss BM: Patterns of monoclonal gammopathy of undetermined significance and multiple myeloma in various ethnic/racial groups: Support for genetic factors in pathogenesis. Leukemia 23:1691-1697, 2009

18. Ailawadhi S, Aldoss IT, Yang D, et al: Outcome disparities in multiple myeloma: A SEER-based comparative analysis of ethnic subgroups. Br J Haematol 158:91-98, 2012
19. Waxman AJ, Mink PJ, Devesa SS, et al: Racial disparities in incidence and outcome in multiple myeloma: A population-based study. Blood 116:5501-5506, 2010
20. Sultan S, Irfan SM, Parveen S, et al: Multiple myeloma: A retrospective analysis of 61 patients from a tertiary care center. Asian Pac J Cancer Prev 17:1833-1835, 2016
21. Lu J, Lu J, Chen W, et al: Clinical features and treatment outcome in newly diagnosed Chinese patients with multiple myeloma: Results of a multicenter analysis. Blood Cancer J 4:e239, 2014
22. Hameed A, Ali J, Munawar K, et al: Characteristics and outcomes of patients with multiple myeloma: Data from a developing country. Med J Islam Republic Iran 32:1-5, 2018
23. Vasquez J, Ruiz R, Aliaga K, et al: Cyclophosphamide, thalidomide, and dexamethasone as initial therapy for patients with newly diagnosed multiple myeloma in a middle-income country: 7-Year follow-up. JCO Glob Oncol 7:1199-1205, 2021
24. Kim K, Lee JH, Kim JS, et al: Clinical profiles of multiple myeloma in Asia—An Asian Myeloma Network study. Am J Hematol 89:751-756, 2014
25. Becker N: Epidemiology of multiple myeloma. Recent Results Cancer Res 183:25-35, 2011
26. Rosiñol L, Oriol A, Teruel AI, et al: Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: A randomized phase 3 PETHEMA/GEM study. Blood 120:1589-1596, 2012
27. Lonial S, Jacobus S, Fonseca R, et al: Randomized trial of lenalidomide versus observation in smoldering multiple myeloma. J Clin Oncol 38:1126-1137, 2020
28. Landgren CO, Chari A, Cohen YC, et al: Daratumumab monotherapy for patients with intermediate-risk or high-risk smoldering multiple myeloma: A randomized, open-label, multicenter, phase 2 study (CENTAURUS). Leukemia 34:1840-1852, 2020
29. Dimopoulos MA, Moreau P, Terpos E, et al: Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Hemasphere 5:e528, 2021
30. Cavo M, Gay F, Beksac M, et al: Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): A multicentre, randomised, open-label, phase 3 study. Lancet Haematol 7:e456-e468, 2020
31. Attal M, Harousseau JL, Stoppa AM, et al: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med 335:91-97, 1996
32. Ganguly S, Mailankody S, Ailawadhi S: Many shades of disparities in myeloma care. Am Soc Clin Oncol Ed Book 39:519-529, 2019
33. Singhal S, Mehta J, Desikan R, et al: Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 341:1565-1571, 1999
34. Richardson P, Anderson K: Thalidomide and dexamethasone: A new standard of care for initial therapy in multiple myeloma. J Clin Oncol 24:334-336, 2006
35. Moreau P, Hulin C, Macro M, et al: VTD is superior to VCD prior to intensive therapy in multiple myeloma: Results of the prospective IFM2013-04 trial. Blood 127:2569-2574, 2016
36. Cavo M, Tacchetti P, Patriarca F, et al: Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: A randomised phase 3 study. Lancet 376:2075-2085, 2010
37. Usmani SZ, Hoering A, Cavo M, et al: Clinical predictors of long-term survival in newly diagnosed transplant eligible multiple myeloma—An IMWG Research Project. Blood Cancer J 8:123, 2018
38. Chan HSH, Milne RJ: Impact of age, sex, ethnicity, socio-economic deprivation and novel pharmaceuticals on the overall survival of patients with multiple myeloma in New Zealand. Br J Haematol 188:692-700, 2020
39. Xu L, Wang X, Pan X, et al: Education level as a predictor of survival in patients with multiple myeloma. BMC Cancer 20:737, 2020
40. Intzes S, Symeonidou M, Zagoridis K, et al: Socioeconomic status is globally a prognostic factor for overall survival of multiple myeloma patients; synthesis of studies and review of the literature: SES as prognostic factor for myeloma survival. Mediterr J Hematol Infect Dis 13:e2021006, 2020
41. Blom JW, Doggen CJM, Osanto S, et al: Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 293:715-722, 2005
42. Diep R, Garcia D: Does aspirin prevent venous thromboembolism? Hematology Am Soc Hematol Educ Program 2020:634-641, 2020
43. 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 28:1122-1128, 2014
44. Hewamana S, Skandarajah T, Jayasinghe C, et al: Blood cancer care in a resource limited setting during the Covid-19 outbreak; a single center experience from Sri Lanka. PLoS One 16:e0256941, 2021