Journal on Oncology

www.journalononcology.org

Research Article

Open Access, Volume 4

Revealing the Correlation Between Multiple Myeloma and Frailty: Contemporary Perspectives and In-Depth Insights

Saad Javaid, MD[1]*; Kelly Frasier, DO, MS[2]; Olivia Carll, BS[3]; Turkan Banu Karatas, BA[4]

[1]Wyckoff Heights Medical Center, New York, USA.

[2]Nuvance Health/Vassar Brothers Medical Center, USA.

[3]Lake Erie College of Osteopathic Medicine, USA.

[4]Emory University School of Medicine, USA.

Abstract

Aim of study: The research sought to assess the association between frailty and hospitalized individuals with a diagnosis of multiple myeloma.

Materials and methods: The National Inpatient Sample database for 2019-2020 was queried to identify individuals over 18 years diagnosed with multiple myeloma, utilizing the appropriate ICD-10 codes. The cohort was further divided into patients with and without frailty. Multivariate linear and logistic regression analysis was performed to assess the association between frailty and multiple myeloma and the impact of frailty on outcomes in patients hospitalized with multiple myeloma.

Results: The study included a cohort of 48,340 patients with multiple myeloma, encompassing 9,605 individuals (19%) diagnosed with frailty. The mortality risk for patients with frailty was observed to be twice that of their non-frail counterparts (OR 2.06, P<0.001). Additionally, patients with frailty experienced significantly extended lengths of stay (+2.49 days, P<0.001) and higher total costs of hospitalization (+USD 29464, P<0.001) compared to those without frailty. Further, frailty emerged as a significant risk factor for several adverse outcomes, including sepsis (OR 1.61, P<0.001), acute respiratory failure (OR 1.53, P<0.001), intensive care unit admission (OR 1.41, P=0.02), constipation (OR 1.17, P=0.025), anemia (OR 1.26, P<0.001), pneumonia (OR 1.35, P=0.009), osteoporosis (OR 1.39, P= 0.018), and consultations for palliative care (OR 2.17, p<0.001).

Conclusion: Frailty is a strong and independent predictor of adverse clinical outcomes in patients hospitalized with multiple myeloma.

Introduction

Multiple Myeloma (MM) is a hematologic malignancy described as a plasma cell dyscrasia, which is the neoplastic proliferation of plasma cells. It is characterized by osteolytic lesions, hypercalcemia, anemia, renal insufficiency, monoclonal proteins in serum or urine, and increased bone marrow plasma cells.

Epidemiologically, multiple myeloma is a rare disease, making up around 1.8% of all malignancies, with an estimated number of 35730 new cases in 2023. In the SEER data, the lifetime risk of getting multiple myeloma in the US was reported as 0.76% [1]. Among hematologic malignancies, it is the second most common after lymphoma. The median age of diagnosis is 66-70 years, and

Manuscript Information: *Received: Dec 21, 2023; Accepted: Jan 16, 2024; Published: Jan 23, 2024*

Correspondance: *Saad Javaid, Wyckoff Heights Medical Center, New York, USA. Email: SJavaid@wyckoffhospital.org*

Citation: *Javaid S, Frasier K, Carll O, Karatas TB. Revealing the Correlation Between Multiple Myeloma and Frailty: Contemporary Perspectives and In-Depth Insights. J Oncology. 2024; 4(1): 1123.*

it is scarce in individuals younger than 30. There is a higher prevalence in males, African Americans, and obese individuals. Lastly, while not considered a genetic disease, a few cases are familial [2].

Myeloma is associated with poor morbidity and mortality; however, in the last decade, the mortality rates have decreased due to the advancement of novel therapies. The 5-year survival of myeloma patients diagnosed between 2013-2019 was reported to be 59.8%, comprising 2.1% of all cancer deaths [1].

Hematologic malignancies are often more prevalent in the older adult population, and their diagnosis is closely associated with age. However, it's essential to recognize that age alone may not fully capture an individual's health condition. Consequently, there is a growing emphasis on integrating geriatric assessments and tools into standard oncology care for these patients. Clinicians have discerned that frailty plays a crucial role as a predictor of unfavorable outcomes in older adults diagnosed with hematological malignancy.

Using a frailty index provides a more comprehensive picture than using age as a predictor of patient outcomes. It helps to identify prognostic groups, adjust treatment modalities and interventions, and improve quality of life based on the frailty predictors of patients [3]. However, evidence regarding the association between frailty and clinical outcomes in patients with multiple myeloma is limited, and our study specifically analyzed patients with multiple myeloma and how frailty impacts this cohort in terms of mortality and other adverse hospital outcomes.

Several frailty scales have been used in different studies, such as the Geriatric 8 (G8), comprehensive geriatric assessment Clinical Frailty Scale, and Fried frailty score. In our analysis, we utilized the Johns Hopkins Adjusted Clinical Groups frailty-defining diagnosis based on 10 clusters of frailty-defining diagnoses. This scale has gained recent prominence due to its use in electronic records and perceived objectivity, leading to increased accuracy.

Materials and methods

Data source: Our study relied on the data provided by the NIS database, which was developed as an integral component of the Healthcare Cost and Utilization Project (HCUP), generously sponsored by the Agency for Healthcare Research and Quality (AHRQ). This massive all-payer inpatient healthcare database offers a wealth of public information to researchers and boasts an impressive sample size that approximates 20% of stratified discharges from community hospitals across America [4]. Using a systematic sampling design, this comprehensive resource is compiled from state-initiated patient databases to create unique discharge records containing critical medical details, including primary and secondary diagnoses along with procedures performed during hospitalization. In addition to the above-mentioned details, demographic information, comorbidities, severity of illness, and mortality risk based on All Patient Refined Diagnosis-Related Groups (APR-DRG), Length of Hospital Stay (LOS), teaching status, hospital location, geographic region of the hospital, as well as an estimated median household income quartile determined by the patient's zip code, are also included in each record. Furthermore, primary payer information, along with discharge disposition and in-hospital mortality, are also documented.

Study design and population: This retrospective cohort study investigated adult patients (18 years old and older) hospitalized with multiple myeloma during the 2019 and 2020 calendar year with or without frailty. The dataset was stratified into two cohorts: one comprising individuals diagnosed with frailty and the other consisting of those without frailty. The International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10 CM) was utilized to accurately identify the primary and secondary diagnoses. The Johns Hopkins Adjusted Clinical Groups encompass a comprehensive set of 10 distinct clusters of diagnoses that identify and define the state of frailty in patients. Utilizing the frailty-defining diagnosis indicator, patients were carefully categorized into frail or non-frail groups based on a thorough assessment.

Outcomes: The study's primary focus was the assessment and comparison of mortality rates between two groups, but it also delved into various secondary endpoints to gain a deeper understanding of patient outcomes. In addition to mortality rates, the study evaluated metrics such as length of hospitalization and total hospital charges, providing insight into resource utilization patterns within each population. The analysis also included the study of critical health complications alongside the primary endpoint, encompassing sepsis, acute respiratory failure, intensive care unit admission, constipation, anemia, pneumonia, osteoporosis, and consultations for palliative care. Furthermore, the Charlson comorbidity index—particularly useful in accounting for confounding factors—was compared between patients with concomitant frailty and those without.

Statistical analysis: The statistical analysis for this study was conducted meticulously to ensure the findings' reliability and validity. The software program Stata 17 was used with weighted samples per Healthcare Cost and Utilization Project regulations when using the NIS database. Descriptive statistics and inferential tests were employed to understand the collected data better. Mean values and standard deviations were used to report continuous variables, while categorical variables were expressed as percentages. The outcomes for continuous variables were evaluated using «Student's t-test,» and «The chi-square test» was applied to categorical variables. Additionally, odds ratios for all outcomes were computed and appropriately adjusted based on age, gender, ethnicity, insurance coverage status, and hospital characteristics in a regression analysis; a p-value of 0.05 was established as the critical level for determining statistical significance.

Results

The study involved a cohort of 48,340 patients diagnosed with multiple myeloma. Among them, 9,605 individuals (19%) were identified as frail, while the remaining 38,735 patients did not exhibit signs of frailty. It was observed that the percentage of frail individuals was notably higher among those aged over 65 years, whereas fewer instances of frailty were found in younger age groups (66.01% vs 52.23%, $p<0.001$). When considering race as a factor, it became evident that the Black population had a higher proportion of patients with frailty compared to other racial groups (27.89% vs 23.46%, $p=0.003$). Moreover, a substantial number of frail patients exhibited a Charlson Comorbidity score indicating three or more comorbid conditions (71% vs 61.04%, $p<0.001$). In terms of insurance coverage and healthcare utilization patterns, Medicare enrollment was more prevalent among Frail patients

(65.14% vs 51.19%, p<0.001), whereas Medicaid and Private insurance had larger percentages within the non-frail group (9.02% vs 7.05% & 37.79% vs 26.16% respectively, p<0.001). Fluid and Electrolyte disorders were more prevalent in the Frail group (64.24% vs 52.63%, p<0.001). In contrast, non-frail patients had a higher prevalence of Hypertension (37.35% vs 31.7%, p<0.001). Furthermore, a larger percentage of frailty patients were discharged to skilled nursing facilities or home with home health care support (3.34% vs 2.63% and 37.59% vs 22.69% respectively, p<0.001). (Table 1).

Table 1: Comparison of baseline characteristics of multiple myeloma patients with and without frailty.

	Myeloma without frailty	Myeloma with frailty	P-Value
No. of patients	38735	9605	
Patient characteristics			
Gender (%)			P=0.824
Male	21769 (56.2)	5370 (55.91)	
Female	16966 (43.8)	4235 (44.09)	
Age distribution (%)			P<0.001
18-35	306 (0.79)	35 (0.36)	
36-45	1515 (3.91)	210 (2.19)	
46-64	16683 (43.07)	3020 (31.44)	
>65	20231 (52.23)	6340 (66.01)	
Race (%)			P=0.003
White	24116 (62.26)	5763 (60)	
Black	9087 (23.46)	2679 (27.89)	
Hispanic	4114 (10.62)	842 (8.77)	
Other	1418 (3.66)	321 (3.34)	
Median household income national quartile for patient zip code (%)			P=0.715
$1-$49,999	10172 (26.26)	2556 (26.61)	
$50,000-$64,999	9145 (23.61)	2314 (24.09)	
$65,000-$85,999	9955 (25.7)	2329 (24.25)	
>$86,000	9463 (24.43)	2406 (25.05)	
Charlson comorbidity index (%)			P<0.001
2	15091 (38.96)	2785 (29)	
3 or more	23644 (61.04)	6820 (71)	
Insurance provider (%)			P<0.001
Medicare	19828 (51.19)	6257 (65.14)	
Medicaid	3494 (9.02)	677 (7.05)	
Private	14638 (37.79)	2513 (26.16)	
Uninsured	775 (2)	159 (1.66)	
Comorbidities (%)			
Hypertension	14468 (37.35)	3045 (31.7)	P<0.001
Diabetes mellitus	6968 (17.99)	1585 (16.5)	P=0.140
Fluid and electrolyte disorders	20386 (52.63)	6170 (64.24)	P<0.001
Chronic kidney disease			
Stage 2	511 (1.32)	150 (1.56)	P=0.472
Stage 3	3509 (9.06)	1035 (10.78)	P = 0.032
Stage 4	1476 (3.81)	500 (5.21)	P = 0.0062
Stage 5	198 (0.51)	90 (0.94)	P = 0.030
ESRD	2142 (5.53)	555 (5.78)	P = 0.695
Hyperlipidemia (HLD)	11454 (29.57)	2780 (28.94)	P = 0.609
Smoking	132 (0.34)	20 (0.21)	P = 0.357
Discharge disposition (%)			P<0.001
Home	28648 (73.96)	5608 (58.39)	
Home with home health	8789 (22.69)	3611 (37.59)	
Skilled nursing facility	1019 (2.63)	321 (3.34)	
Against medical advice	279 (0.72)	65 (0.68)	
Hospital characteristics (%)			
Bed size of hospital (STRATA)			P = 0.573
Small	5450 (14.07)	1300 (13.53)	
Medium	7693 (19.86)	2040 (21.24)	
Large	25592 (66.07)	6265 (65.23)	
Hospital location			P = 0.826
Rural	1170 (3.02)	300 (3.12)	
Urban	37565 (96.98)	9305 (96.88)	
Hospital teaching status			P = 0.189
Non-teaching hospital	4427 (11.43)	1215 (12.65)	
Teaching hospital	34308 (88.57)	8390 (87.35)	
Region of hospital			P = 0.503
Northeast	8243 (21.28)	2280 (23.74)	
Midwest	8638 (22.3)	2040 (21.24)	
South	14855 (38.35)	3610 (37.58)	
West	6999 (18.07)	1675 (17.44)	

Table 2: Comparison of mortality in multiple myeloma patients with and without Frailty.

	(%) of Myeloma without frailty		(%) of Myeloma with frailty	
	Dead	**Alive**	**Dead**	**Alive**
Mortality	0.035	0.96	0.081	0.91
	Myeloma with and without Frailty			
	Odds Ratio	**95% CI**	**P value**	
Mortality				
Unadjusted odds ratio (Univariate logistic regression)	2.45	(1.95- 3.07)	P<0.001	
Adjusted odds ratio (Multivariate logistic regression)	2.06	(1.60-2.65)	P<0.001	

CI: Confidence Interval.

The univariate analysis showed that frail patients experienced a higher mortality rate (OR 2.45 95% CI: 1.95-3.07, p<0.001). Subsequently, following adjustments for confounding variables and conducting multivariate regression analysis, it was established that frailty is associated with a twofold increase in the risk of mortality and serves as an independent predictor of mortality in Multiple myeloma patients (OR 2.06, 95% CI: 1.60-2.65, p<0.001) (Table 2).

Furthermore, the multivariate regression analysis revealed that frailty correlates with prolonged length of stay (+2.49 Days, 95% CI: 1.80-3.17, p<0.001) and increased total cost of hospitalization (+29464 USD, 95% CI: 16971-41957, p<0.001) (Table 3).

Table 3: Comparison of length of stay and total cost of hospitalization in multiple myeloma patients with and without frailty.

	Myeloma with and without frailty		
Length of hospitalization (days)	**Coefficient**	**95% CI**	**P value**
LOS Days (Univariate linear Regression)	2.48	(1.68-3.12)	P<0.001
LOS Days (Multivariate linear Regression)	2.49	(1.80-3.17)	P<0.001
Total hospital cost (USD)			
TOTCHG USD (Univariate linear Regression)	26885	(14162-39607)	P<0.001
TOTCHG USD (Multivariate linear Regression)	29464	(16971-41957)	P<0.001

LOS: Length of Stay; TOTCHG: Total Charges; CI: Confidence Interval; USD: United States Dollar.

Moreover, it was found that frailty heightened the risk of several secondary adverse events during hospitalization; these included sepsis (OR 1.61, 95% CI: 1.27-2.04, p<0.001), Acute Respiratory failure (OR 1.41, 95% CI: 1.26-1.87, p<0.001), Admission to ICU (OR 1.41, 95% CI 1.13-1.76, p=0.002), Acute kidney injury (OR 1.15, 95% CI: 1.11-1.31, p=0.035), Pneumonia (OR 1.35, 95% CI: 1.07-1.70, p=0.009), Constipation (OR 1.17, 95% CI: 1.12-1.34, p=0.025), Anemia (OR 1.26, 95% CI: 1.11-1.43, p<0.001), and involvement of Palliative care (OR 2.17, 95% CI: 1.84-2.57, p<0.001). However, no significant difference was noted in the incidence rates related to Major Depressive Order (OR 0.94, 95% CI: 0.79-1.12, p=0.537), altered mental status (OR 1.28, 95% CI: 0.69-2.36, p=0.417) or hypercalcemia (OR 1.17, 95% CI: 0.99-1.37, p=0.056). (Tables 4 & 5).

Table 4: Comparison of secondary outcomes in multiple myeloma patients with and without frailty.

Secondary outcomes	Myeloma without frailty (%)	Myeloma with frailty (%)	Unadjusted OR (95%CI)
Sepsis	0.0494	0.0848	1.78(1.42-2.23)
Intensive Care Unit (ICU)	0.0506	0.0744	1.50(1.20- 1.88)
Acute respiratory failure	0.0547	0.0957	1.82(1.51- 2.20)
Acute kidney injury	0.349	0.4492	1.51(1.34-1.71)
Major Depressive Disorder	0.1119	0.1061	0.94(0.79- 1.11)
Altered mental status	0.0068	0.0119	1.75(1.01- 3.02)
Constipation	0.208	0.2269	1.11(0.98-1.26)

Discussion

Frailty predisposes multiple myeloma patients to increased medical comorbidities due to decreased physiological reserve. Elderly patients are at risk of increased adverse effects, including mortality from associated treatment medications [5]. Risk for frailty in older patients with cancer receiving chemotherapy includes living alone, stage of disease, and education level [6].

Table 5: Adjusted analysis of secondary outcomes in multiple myeloma patients with and without frailty.

	Multivariate regression analysis of secondary outcomes		
	Odds ratio	**95% Confidence Interval**	**P-value**
Secondary outcomes			
Sepsis	1.61	(1.27- 2.04)	P<0.001
Intensive Care Unit (ICU)	1.41	(1.13-1.76)	P=0.002
Acute respiratory failure	1.53	(1.26-1.87)	P<0.001
Acute kidney injury	1.15	(1.11-1.31)	P=0.035
Major Depressive Disorder	0.94	(0.79-1.12)	P=0.537

Our retrospective study, focusing on a substantial cohort of 48340 patients diagnosed with multiple myeloma, offered critical insights into the impact of frailty on clinical outcomes. The findings revealed a considerable prevalence of frailty, affecting 19% of the studied population. This establishes frailty as a noteworthy concern in the context of multiple myeloma, prompting an exploration of its ramifications.

The findings of our study revealed a significant association between frailty and mortality in patients with multiple myeloma, indicating that frailty serves as an independent predictor of mortality. In our research, frailty contributed to a more complex medical course, including ICU admission and extended length of stay, which further supports the association with increased total hospital costs. ICU admission requires more stringent monitoring, increasing labor and time costs. Comorbidities require improved disease management, which takes time and can extend the length of admission. Similarly, our results demonstrated the development of acute respiratory failure in patients with frailty. The descriptive statistical multivariable logistic regression among 1157 patients by Hope et al. signifies our findings [7]. Their study showed that frailty increased hospital course and mortality compared to patients without frailty. Similarly, a study completed by Muscedere et al. reported 30% of adult ICU admissions to have frailty and the association with worse outcomes, including increased mortality [8].

Our study interpreted the impact of frailty in the development of adverse outcomes and revealed the correlation of frailty with increased palliative care involvement. Palliative care professionals support individuals with complex medical conditions and associated comorbidities to improve their quality of life. As demonstrated in this article, patients with frailty have an increased association with multiple comorbidities. Therefore, the need for increased support in managing these conditions and improving life quality can be understood. These findings support previous research by Stow et al. that provided evidence of the multiple physical and psychosocial needs of patients with frailty and, therefore, the benefits of care from palliative services [9].

The results of our study demonstrate a clear relation between frailty/multiple myeloma and sepsis—findings that indicate severe comorbidity and risk of more complex hospitalization. Other studies investigating frailty and sepsis have resulted in similar conclusions. Lee et al. investigated 936 hospitalized patients using multivariable logistic regression analysis and found a statistically significant increase in in-hospital mortality in frail patients with

sepsis compared to non-frail patients [10].

Our study findings of increased association of patients with frailty developing acute respiratory failure concurred with the Galet et al. study, which investigated the implications of frailty and its increased association with acute respiratory failure using multivariate analyses among 851 patients [11]. Iwai-Saito et al. conducted a cross-sectional study using the Japan Gerontological Evaluation Study, which enrolled 177,991 patients >/= 65 years and concluded that frailty was associated with increased hospitalizations due to pneumonia in this patient population [12].

Results of our study support these findings in that frailty was associated with worse hospital outcomes, specifically a significant association with the development of acute respiratory failure and pneumonia. The contribution of the frailty index measurements, including exhaustion, low energy expenditure, and decreased strength, may worsen pulmonary function as adequate chest wall expansion requires energy expenditure through muscle use and oxygen exchange.

A study by Liu et al. using a bowel health questionnaire and co-variables evaluation provided evidence that the frailty index is more significant in those with constipation and diarrhea [13]. Further studies by Konradsen et al. have shown that hospitalization is associated with an increased percentage of constipation diagnoses as well as an increase in the number of laxatives prescribed. In support of these results, analysis done in our study revealed that patients with frailty had increased constipation compared to patients without frailty. Activity level and energy expenditure affect gastrointestinal function, including transit time. Patients with Frailty have decreased energy expenditure, often perpetuated during hospitalization due to reduced mobility, comorbid conditions, and change to routine [14]. Therefore, frailty is a combined factor that increases the association of constipation, particularly in hospitalized patients with multiple myeloma.

The regression analysis of frailty and osteoporosis by Sternberg et al. resulted in evidence supporting the use of frailty status to predict a decrease in bone mineral density after one year [15]. The results from our study further support these findings, as we demonstrated frailty as a significant risk for adverse outcomes, including osteoporosis. Weight-bearing increases bone mineral density and can prevent further bone loss [16]. Therefore, weight loss and slowed walking speed in frailty patients can contribute to an increased likelihood of bone mineral density reduction and osteoporosis.

Beyond mortality, the study sheds light on the broader consequences of frailty in the hospital setting. These findings underscore the economic burden of frailty, prompting considerations for resource allocation and healthcare planning. The extended lengths of stay and heightened costs may indicate the complexity and severity of clinical management required for frail patients, necessitating a more comprehensive and potentially resource-intensive approach to their care.

In conclusion, this study provides robust evidence that frailty is a potent and independent predictor of adverse clinical outcomes in patients hospitalized with multiple myeloma. Acknowledging frailty as a critical factor in the clinical landscape of multiple myeloma is pivotal for healthcare practitioners, necessitating tailored strategies and interventions to mitigate its impact and improve patient outcomes.

The comprehensive nature of the NIS database provides a strong foundation for uncovering valuable insights and trends related to the healthcare landscape. By delving into the data derived from a wide range of patient demographics and medical settings, the study benefits from a robust representation of the population of the United States. Furthermore, the meticulous application of multivariate regression analysis addresses potential confounding factors, thereby enhancing the credibility and relevance of the findings. This approach enables a more nuanced understanding of the interplay between various variables and their impact on patient outcomes, contributing to a deeper comprehension of critical care dynamics. Nevertheless, while NIS provides valuable insights, it also has its limitations. It does not capture the severity of the disease or specific diagnostic methods used. Additionally, crucial data on pharmaceutical therapies administered during hospitalization is absent. The use of ICD-10 codes to identify patients may lead to coding errors. Furthermore, it lacks the ability to assess the severity of frailty, and overall numbers may be underreported. Another limitation is that this database only includes current hospitalization data, making it unable to evaluate readmissions. Hence, further validation in a prospective cohort study with more comprehensive clinical information about treatment and long-term mortality is required for robust findings from this study.

Conclusion

In conclusion, our study presents compelling evidence that frailty is a formidable and independent predictor of adverse clinical outcomes in hospitalized patients with multiple myeloma. The two-fold increase in mortality risk among frail individuals emphasizes the gravity of frailty as a prognostic factor, underscoring its significance in clinical decision-making. Moreover, the study explains the broader implications of frailty, revealing extended hospital stays and increased costs, highlighting the economic burden associated with this condition. The comprehensive exploration of adverse outcomes, ranging from sepsis to ICU admissions, further emphasizes the multifaceted impact of frailty on the health status of multiple myeloma patients.

References

1. SEER Lifetime Risk (Percent) of Being Diagnosed with Cancer by Site and Race/Ethnicity: Both Sexes. 18 SEER Areas, 2012-2014 (Table 1.15) National Cancer Institute, Bethesda, MD. 2018. https://seer.cancer.gov/csr/1975_2014/results_merged/topic_lifetime_risk.pdf.

2. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. Semin Oncol. 2016; 43(6): 676-681. doi: 10.1053/j.seminoncol.2016.11.004. Epub 2016 Nov 10. PMID: 28061985; PMCID: PMC5283695.

3. Möller MD, Gengenbach L, Graziani G, Greil C, Wäsch R, Engelhardt M. Geriatric assessments and frailty scores in multiple myeloma patients: a needed tool for individualized treatment? Curr Opin Oncol. 2021; 33(6): 648-657. doi: 10.1097/CCO.0000000000000792. PMID: 34534141; PMCID: PMC8528138.

4. Khera R, Angraal S, Couch T, et al. Adherence to Methodological Standards in Research Using the National Inpatient Sample.

JAMA. 2017; 318(20): 2011-2018. https://doi.org/10.1001/jama.2017.17653.

5. Bringhen S, Mateos MV, Zweegman S, et al. Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials. Haematologica. 2013; 98(6): 980-987. doi: https://doi.org/10.3324/haematol.2012.075051.

6. Cohen HJ, Smith D, Sun CL, et al. Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. 2016; 122(24): 3865-3872. doi: https://doi.org/10.1002/cncr.30269.

7. Hope AA, Adeoye O, Chuang EH, Hsieh SJ, Gershengorn HB, Gong MN. Pre-hospital frailty and hospital outcomes in adults with acute respiratory failure requiring mechanical ventilation. Journal of Critical Care. 2018; 44: 212-216. doi: https://doi.org/10.1016/j.jcrc.2017.11.017.

8. Muscedere J, Waters B, Varambally A, et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Medicine. 2017; 43(8): 1105-1122. doi: https://doi.org/10.1007/s00134-017-4867-0.

9. Stow D, Spiers G, Matthews FE, Hanratty B. What is the evidence that people with frailty have needs for palliative care at the end of life? A systematic review and narrative synthesis. Palliative Medicine. 2019; 33(4): 399-414. doi: https://doi.org/10.1177/0269216319828650.

10. Lee HY, Lee J, Jung YS, et al. Preexisting Clinical Frailty Is Associated with worse Clinical Outcomes in Patients with Sepsis. Critical Care Medicine. 2021. Publish Ahead of Print. doi: https://doi.org/10.1097/ccm.0000000000005360.

11. Galet C, Lawrence K, Lilienthal D, et al. Admission Frailty Score Are Associated with Increased Risk of Acute Respiratory Failure and Mortality in Burn Patients 50 and Older. Journal of Burn Care & Research. Published online. 2022. doi: https://doi.org/10.1093/jbcr/irac12.

12. Iwai-Saito K, Shobugawa Y, Aida J, Kondo K. Frailty is associated with susceptibility and severity of pneumonia in older adults (A JAGES multilevel cross-sectional study). Scientific Reports. 2021; 11(1). doi: https://doi.org/10.1038/s41598-021-86854-3.

13. Liu X, Wang Y, Shen L, et al. Association between frailty and chronic constipation and chronic diarrhea among American older adults: National Health and Nutrition Examination Survey. BMC Geriatrics. 2023; 23(1). doi: https://doi.org/10.1186/s12877-023-04438-4.

14. Konradsen H, Lundberg V, Florin J, Boström AM. Prevalence of constipation and use of laxatives, and association with risk factors among older patients during hospitalization: a cross sectional study. BMC Gastroenterology. 2022; 22(1). doi: https://doi.org/10.1186/s12876-022-02195-z.

15. Sternberg SA, Levin R, Dkaidek S, Edelman S, Resnick T, Menczel J. Frailty and osteoporosis in older women—a prospective study. Osteoporosis International. 2013; 25(2): 763-768. doi: https://doi.org/10.1007/s00198-013-2471-x.

16. Benedetti MG, Furlini G, Zati A, Letizia Mauro G. The Effectiveness of Physical Exercise on Bone Density in Osteoporotic Patients. BioMed Research International. 2018; 2018(4840531): 1-10. doi: https://doi.org/10.1155/2018/4840531.