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Association of frailty with clinical outcomes in myelofibrosis: a retrospective cohort study

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Summary

There is limited understanding of the impact of frailty on clinical outcomes in patients with myelofibrosis (MF). In this retrospective cohort study on 439 chronic phase MF patients [mean age: 68·7 ± 12 years; median follow-up: 3·4 years (IQR 0·4–8·6)] from 2004 till 2018, we used a 35-variable frailty index (FI) to categorise patient's frailty status as fit (FI < 0·2, reference), prefrail (FI 0·2–0·29) or frail (FI ≥ 0·3). The association of frailty with overall survival (OS) and cumulative JAK inhibitor (JAKi) therapy failure was measured using hazard ratio (HR, 95% CI). In multivariable analysis, prefrail (HR 1·7, 1·1–2·5) and frail patients (HR 2·9, 1·6–5·5), those with higher DIPSS score (HR 2·5, 1·6–3·9) and transfusion dependency (HR 1·9, 1·3–2·9) had shorter OS. In a subset analysis of patients on JAKi treatment (n = 222), frail patients (HR 2·5, 1·1–5·7), patients with higher DIPSS score (HR 1·7, 1·0–3·1) and transfusion dependence (HR 1·7, 1·1–2·7) had higher cumulative incidence of JAKi failure. Age, comorbidities, ECOG performance status, and MPN driver mutations did not impact outcomes. Thus, higher frailty scores are associated with worse OS and increased JAKi failure in MF, and is a superior indicator of fitness in comparison to age, comorbidities, and performance status.

Keywords: myelofibrosis, frailty, prognostic factors, JAK inhibitors.

Introduction

The diverse fitness levels of older cancer patients pose a therapeutic and prognostic challenge.[1] The American Society of Clinical Oncology recommends performing geriatric assessment for all cancer patients ≥ 65 years before starting treatments.[2] The reduction of physiological reserve across multiorgan systems with ageing is not identical for individuals of the same chronological age.[3] Thus, when faced with health challenges, their ability to respond and rebound using this reserve markedly differs. This ability, or the lack thereof, is measured using the concept of frailty.[4] Greater frailty (or lower reserve) is associated with exceptionally higher mortality, health resource utilisation, post-operative complications, and chemotherapy toxicity.[5-7] In myelofibrosis, where median age at diagnosis is 70 years, the contribution of frailty to clinical outcomes is not known.

Rockwood and colleagues have operationalised the measurement of frailty using a clinical index consisting of deficits across various domains of functioning, such as disabilities, diseases, physical and cognitive impairments, and psychosocial factors.[8,9] This multidimensional nature of frailty makes it a global and better indicator of at-risk older patients than chronological age,[10] comorbidities[11] or performance scores[12] alone. Several clinical factors that determine higher frailty levels are also seen in myelofibrosis. First, the MPN driver and other myeloid malignancy mutations in myelofibrosis increase the expression of inflammatory genes resulting in a higher risk of cardiovascular disease and comorbidities.[13] Second, the excessive cytokine release from this inflammation results in high symptom burden, lower physical activity, and cachexia. Third, psychosocial issues such as depression and social isolation are higher in myelofibrosis patients when compared to the general population.[14-16] Given these associations, a high prevalence of frailty is expected in this disease compared with age-matched controls, but both its prevalence and impact upon clinical outcomes have not been investigated to date. The clinical decisions in myelofibrosis depend on the prognostic scoring systems that use chronological age as a variable of patient characteristics.[17-19] Whether incorporation of a broader measure such as frailty could improve their risk prediction needs to be studied. Further, patients with myelofibrosis on JAK inhibitor (JAKi) therapy have high treatment failure rates because of cytopenias, disease

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progression or loss of response. It is possible that those with higher frailty could have increased JAKi treatment failure, as evident in several other cancers.[20] Frailty is potentially reducible or even preventable.[21] An understanding of its association with survival and treatment failure would therefore help guide future strategies to improve outcomes in myelofibrosis.

Using a 35-item frailty index, we measured frailty and evaluated its impact on overall survival in patients with myelofibrosis in chronic phase. In a subset of patients receiving JAKi therapy, we assessed the effect of frailty on overall survival and JAKi treatment failure. In an exploratory analysis, we analysed the association of driver (*JAK2*, *CALR*, *MPL*) and high-risk (*ASXL1*, *IDH1/2*, *EZH2*, *SRSF2*) molecular mutations with frailty.

Methods

Study design, patients and data sources

We conducted a single centre, retrospective cohort study to include subjects with myelofibrosis in chronic phase (< 10% blasts in peripheral blood and bone marrow[22,23]) from January 2001 till December 2018, seen at Princess Margaret Cancer Center, Toronto, Canada. We included patients with primary, post-polycythaemia vera, post-essential thrombocythaemia), and prefibrotic myelofibrosis at their first visit. Patients in accelerated or blast phase myelofibrosis were excluded. Data were obtained from the prospective myeloproliferative neoplasm study from 2016 onwards (NCT02760238) and by chart review for earlier years. The study was approved by the research ethics board at University Health Network, Toronto, CA (19-5119).

Exposure: assessment of frailty

The main exposure was a diagnosis of frailty and prefrailty, defined using a 35-item frailty index calculated at first visit. A frailty index (FI) counts deficits in health which can be symptoms, signs, diseases, disabilities, or laboratory or radiographic abnormalities. According to Searle *et al.*,[24] these deficits (i) must be associated with health status; (ii) their prevalence must generally increase with age; (iii) they must not saturate too early, and (iv) they must cover a range of health systems. These deficits do not have to be same as in Rockwood's original FI if they satisfy the above conditions. A FI constructed with at least 30 deficits has been shown to be psychometrically robust and sufficiently accurate for predicting adverse outcomes in datasets that might not have been set out to measure frailty.[25] Accordingly, the FI constructed for this study (Figure S1) included deficits (n = 35), such as comorbidities (n = 18), ability to handle daily activities (n = 1), physical performances (n = 2), polypharmacy (n = 1), social support (n = 1), nutrition (n = 1) and abnormal blood tests (n = 11). Every variable was transformed into either 0 (deficit absent) or 1 (deficit present). The FI was calculated as the sum of all deficits in each participant, divided by the sum of all variables evaluated. The FI scores could range from 0 (absence of all deficits) to 1 (presence of all deficits). Patients were categorised as frail if the FI was 0·3 or higher, prefrail if FI was between 0·20–0·29, and fit if FI was < 0·19. These cutoffs were based on previous studies.[24]

Outcome variables

Our primary outcome was all-cause mortality in patients with myelofibrosis in chronic phase. We calculated the survival time from time of first visit to the cancer centre till date of last follow-up or death. Our secondary outcomes were all-cause mortality and time to treatment failure in a subset of patients treated with JAKi therapy. We defined JAKi treatment failure as the time from the start of JAKi therapy to one of the following: treatment discontinuation sub-optimal, loss of spleen response, severe anaemia, thrombocytopenia, progression to accelerated (blast count 10–19%) or blast phase (blast count ≥ 20%), or death due to any cause, as per the Canadian consensus criteria.[26] We censored patients at the date of last follow-up if they did not experience the outcome of interest, or on the day of allogeneic stem cell transplantation. In an exploratory analysis, we measured the association of FI with (i) MPN driver mutations (*JAK2*, *CALR* and *MPL*) in all patients, and (ii) high-risk molecular mutation[27] (*ASXL1*, *IDH1/2*, *EZH2*, *SRSF2*) in patients with availability of targeted next generation sequencing (NGS) at first visit. The details of targeted NGS and variant calling have been previously published.[28].

Covariates

At the first visit to our centre, we collected information on patients' age at the time of diagnosis, sex, disease variables such as haemoglobin, white blood cell count, platelet count, cytogenetics, driver mutation status, dynamic international prognostic scoring system (DIPSS) score, performance status measured using Eastern Cooperative Oncology Group (ECOG) sore and comorbidity burden, using haematopoietic stem cell transplant-comorbidity index (HCT-CI) index. The cut-off for advanced age was chosen as 65 years, based on other widely used risk-scoring systems in myelofibrosis such as IPSS,[17] DIPSS,[18] and DIPSS plus.[19] ECOG performance status was divided into three groups—0, 1, ≥ 2—because there were very few patients with a ECOG of 3 or higher and they were collapsed into a single category. The HCT-CI score was collapsed into three risk groups: 0 (low risk), 1 to 2 (intermediate risk), and three or more (high risk), based on the original publication that validated this risk scoring.[29]

Statistical analysis

We provided descriptive statistics with mean and standard deviation for continuous factors, and frequencies and

percentages for categorical factors. We compared the demographics and clinical characteristics using the ANOVA test for continuous variables, and the Chisq test or Fisher exact test for categorical variables. Our primary outcome was overall survival (OS) which was analysed using Kaplan–Meier curves. We used log rank tests to compare OS between frailty status. To include the effect of potential confounders, we conducted the multivariable Cox proportional-hazards regression model. The covariates in the multivariable model were decided *a priori*, based on the clinical knowledge that they were confounders and were not selected based on a specific *P*-value in the univariate analysis alone. The measure of strength of association between mortality and the predictors was reported using hazard ratios (HRs) and a corresponding 95% confidence interval. For internal validation of our multivariable model, we used a bootstrap approach to obtain optimism-corrected measures of model performance using Harrell's C-index.[30,31] For this, we first assessed the performance of our model in the random bootstrap sample and in the entire cohort to obtain an estimate of optimism. The mean of bootstrapped estimates of optimism was then subtracted from the initial estimate of the C-index to obtain the bootstrap optimism-corrected estimates of performance.

We used Kaplan–Meier curves to analyse our secondary outcome of cumulative JAKi treatment failure. The difference in cumulative incidence estimates for JAKi treatment failure was tested using the log rank test. HRs were calculated to measure the association of covariates in the Cox-proportional hazards model for JAKi treatment failure. For our exploratory analysis of association of molecular mutations with frailty indices, we used two-way ANOVA, and pairwise comparison was done with student *t*-tests. The significance threshold was 0·05 and testing was two-sided. Statistical analyses were conducted using either R (version 3.0.2) or SAS (version 9.4).

Results

Baseline characteristics at first visit and frailty index

Between 2004 and 2018, we identified 439 patients with a diagnosis of myelofibrosis (primary = 229, post-essential thrombocythaemia = 87, post-polycythaemia vera = 66, prefibrotic = 57). Baseline patient and disease characteristics are presented in Table I. The median follow-up of the study cohort was 3·4 years (IQR, 0·4–8·6). The prevalence of frailty was 40·7% [8·4% had FI ≥ 0·3 (frail) and 32·3% had FI 0·2–0·29 (prefrail)]. The median frailty index in fit, prefrail and frail patients was 0·1, 0·2 and 0·3, respectively. Patients were more likely to be frail if they were of an advanced age, had a higher DIPSS, ECOG and HCT-CI score, and were transfusion-dependent. Hypertension was the most common abnormality (Figure S1), followed by hypercholesterolaemia, and liver or gastrointestinal problems. Polypharmacy was noted in 43% of patients, impaired physical function and social isolation in 10%, respectively, and nutritional issues in 5% of patients. The most common laboratory abnormalities were lactate dehydrogenase and urate elevation.

Association of frailty with overall survival in myelofibrosis

A total of 147 patients (33·4%) experienced the primary outcome of interest—death from any one cause. Survival was worse in those with frailty (three years OS: 25·2%, 95% CI, 11·8–54·1%) and prefrailty (three years OS: 59·6%, 95% CI, 50·8–70·1%) compared to fit patients (three years OS: 83·9%, 95% CI, 78·5–89·6%). The Kaplan–Meier survival function showed that frail and prefrail patients had a higher probability of death compared to fit patients (log-rank, $P < 0·001$) (Fig 1A). In univariate analysis (Figure S2), the HR for probability of death was 6·2 (95% CI, 3·7–10·3) for frail and 2·1 (95% CI, 1·5–3·1) ($P < 0·001$) for prefrail, compared to fit patients. Advanced age (≥ 65 years), higher ECOG status (2 or more), higher HCT-CI index, higher DIPSS category and transfusion dependency were all associated with worse survival (all $P < 0·05$). In multivariable Cox regression analysis (Fig 1B), the impact of frailty on mortality remained significant: adjusted HRs for mortality were 1·7 (95% CI, 1·1–2·5) for prefrailty and 2·9 (95% CI, 1·6–5·5) for frailty. Other significant predictors for mortality were intermediate—2/high-risk DIPSS category and transfusion dependency. Type of driver gene mutation, age at diagnosis, gender, comorbidity index (HCT-CI), and performance status (ECOG) did not predict overall survival. Frailty did not show a significant association with leukaemic transformation in a competing risk survival analysis (Figure S3) with HRs of 0·8 (95% CI, 0·4–1·6) for prefrail and 0·4 (95% CI, 0·1–1·9) for frail patients.

We performed an internal validation of our multivariable Cox-proportional hazard model using the bootstrapping method. The optimism-corrected C-index was 0·75, suggestive of good discrimination. In addition, the calibration curve showed that the model was well calibrated (Figure S4).

When a subset analysis was performed according to the DIPSS-risk stratification, prefrail and frail individuals in low-intermediate-1 and intermediate-2 high-risk (Fig 2A) categories had an increased probability of death compared to fit patients ($P < 0·05$). Further, the effect of advanced age on survival was only observed in patients who were fit; however, advanced age did not have an impact on the survival of frail or prefrail patients (Fig 2B).

Association of frailty with overall survival and treatment failure in patients treated with JAK inhibitors in myelofibrosis

A total of 222 patients were treated with JAK inhibitors (ruxolitinib as clinical trial, $n = 78$, ruxolitinib as standard of care, $n = 110$; other novel JAKi agents were used as part of a

Table I. Baseline characteristics of the study cohort according to frailty status.

Characteristic	Total (n = 439)	Fit (n = 260)	Prefrail (n = 140)	Frail (n = 39)	P-value
Patient characteristics					
Frailty Index					
Median (Min, Max)	0·2 (0,0·1)	0·1 (0,0·2)	0·2 (0·2,0·3)	0·3 (0·3,0·5)	<0·0001
Age, years					
Mean (SD)	68·7 (12·8)	65·6 (13·4)	73 (10·5)	73·9 (9·6)	0·0001
Gender, *N* (%)					
Male	259 (59)	138 (53)	89 (64)	32 (81)	0·001
Female	180 (41)	122 (47)	51 (36)	7 (19)	
ECOG, *N* (%)					
0	239 (54)	161 (62)	68 (48)	10 (27)	<0·0001
1	162 (37)	86 (33)	63 (44)	13 (35)	
≥2	38 (9)	13 (5)	11 (8)	14 (38)	
HCT-CI, *N* (%)					
Low	230 (52)	170 (65)	52 (37)	8 (22)	<0·0001
Intermediate	125 (28)	61 (23)	54 (38)	10 (27)	
High	84 (19)	29 (11)	36 (25)	19 (51)	
No. of cardiovascular risk factors, *N* (%)					
0–1	237 (75)	164 (86)	67 (63)	6 (30)	<0·0001
2 or more	81 (25)	27 (14)	40 (37)	14 (70)	
Missing	121	69	35	17	
Period of diagnosis, *N* (%)					
Before 2007	33 (12·7)	17 (12·1)	6 (15·4)	56 (12·8)	0·18
2008–2011	63 (24·2)	32 (22·9)	3 (7·7)	98 (22·3)	
2012–2019	164 (63·1)	91 (65·0)	30 (76·9)	285 (64·9)	
Time to first visit after diagnosis in months, median (IQR)	3·2 (1·4–17·5)	3·0 (1·4–17·6)	4·4 (1·6–14·1)	3·2 (1·4–17·5)	0·24
Disease characteristics					
Transfusion dependent					
No	346 (79)	218 (84)	103 (74)	25 (62)	0·003
Yes	93 (21)	42 (16)	37 (26)	14 (38)	
Platelet count					
$<100 \times 10^9$/l	160 (36)	83 (19)	50 (19)	27 (19)	0·96
WBC count					
$>25 \times 10^9$/l	71 (16)	26 (10)	30 (21)	15 (41)	<0·0001
DIPSS category					
Low/intermediate 1	221 (50)	162 (62)	54 (38)	5 (14)	<0·0001
Intermediate 2/high	218 (50)	98 (38)	88 (62)	32 (86)	
Driver mutation (n = 432)					
JAK2	295 (67)	168 (65)	95 (68)	32 (82)	0·24
CALR	82 (19)	52 (20)	26 (19)	4 (10)	
MPL	26 (6)	21 (8)	5 (4)	0 (0)	
Triple negative	36 (8)	19 (7)	14 (10)	3 (8)	
No. of HMR mutation (n = 199), *N* (%)					
None	95 (48)	62 (52)	34 (46)	4 (26)	0·16
1	59 (30)	34 (29)	18 (27)	7 (47)	
2 or more	45 (22)	23 (19)	18 (27)	5 (27)	
JAK inhibitor, *N* (%)					
Yes	222 (51)	112 (43)	89 (63)	21 (57)	<0·0001
Allo-SCT, N (%)					
Yes	67 (15)	45 (17)	20 (14)	2 (5)	0·15

ECOG, Eastern Co-operative Group scale; HCT-CI, haematopoietic stem cell transplantation-comorbidity index; Cardiovascular risk factors—hypertension, dyslipidaemia, diabetes mellitus, smoking; DIPSS, Dynamic International Prognostic Scoring System; HMR, high-risk molecular mutation; Allo-SCT, allogeneic stem cell transplantation.

clinical trial, n = 34). The two-year mortality (log-rank, P < 0·001) was higher in frail (89·2%, 95% CI, 83·0–95·8%) and prefrail (71·2%, 95% CI, 61·7–82·2%) compared to fit (59·9, 95% CI, 39·3–91·4%) patients as shown by the Kaplan–Meier survival analysis (Fig 3A). The results of univariate analysis are presented in Figure S5. In multivariable

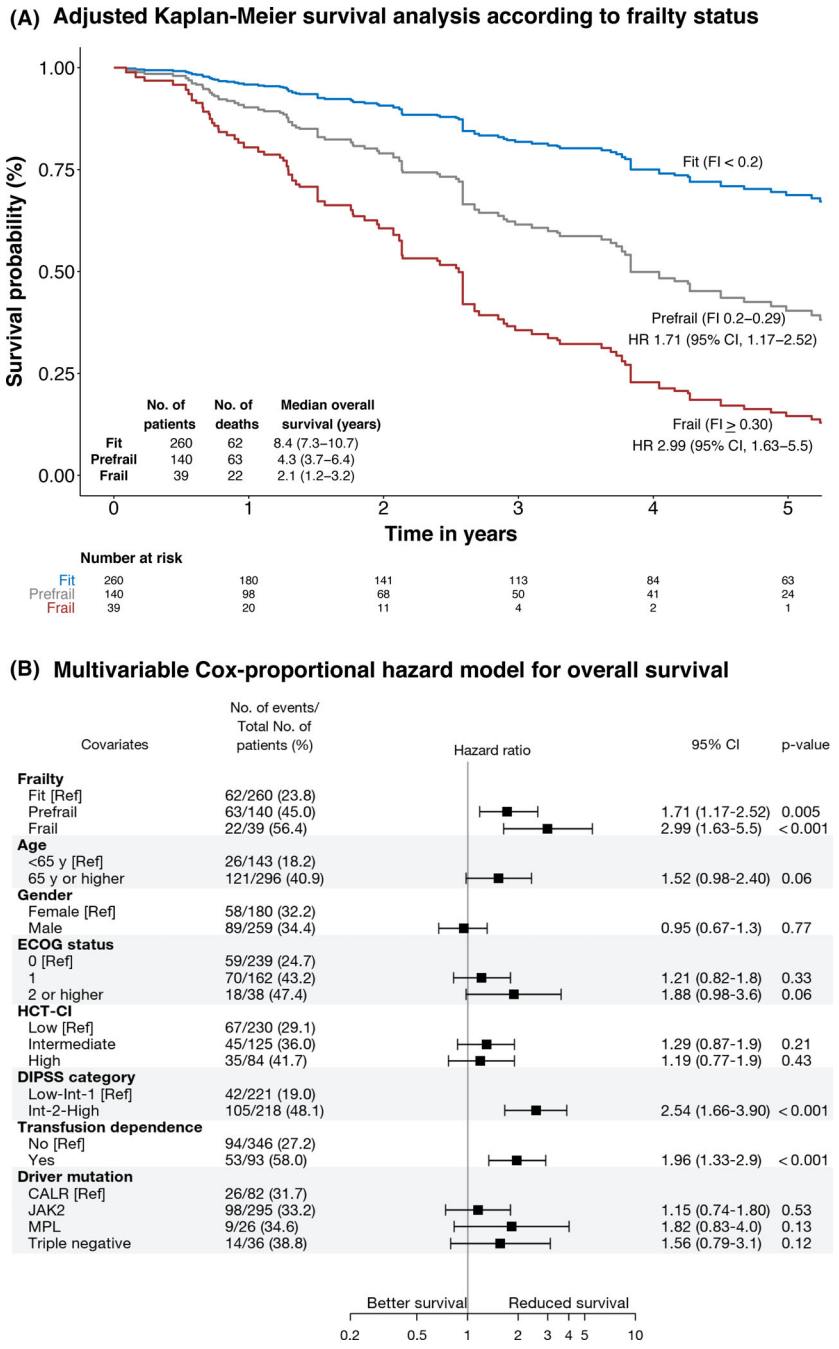

Fig 1. Overall survival in patients with myelofibrosis according to frailty status (n = 439). (A) Overall survival data, from time of first visit, among 439 patients with myelofibrosis, stratified by the frailty status, defined using a 35-item cumulative deficit frailty index. The Kaplan–Meier curves shown were adjusted for the multivariable cox proportional regression model in (B). (B) Forest plot represents the HRs from the multivariable cox regression analysis to determine the association between frailty status and overall survival. For all estimates, $P \leq 0{\cdot}05$ was considered statistically significant. ECOG, Eastern Co-operative Group scale; HCT-CI, haematopoietic stem cell transplant comorbidity index; DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; CI, confidence interval; FI, frailty index. [Colour figure can be viewed at wileyonlinelibrary.com]

Cox-proportional hazard analysis (Fig 3B), prefrail and frail patients, those with DIPSS intermediate-2/high-risk stratification and transfusion dependency were associated with worse overall survival. Out of 222 patients treated with JAKi, 108 patients were noted to have treatment failure. The two-year probability of cumulative JAKi treatment failure was higher in frail patients (54·3%, 95% CI, 24·7–84·0%) and prefrail (54·3%, 95% CI, 29·4–52·1%) compared to fit patients (33·6%, 95% CI, 23·5–43·8%) (log-rank, P = 0·007) (Fig 4A). The results of univariate Cox-proportional analysis

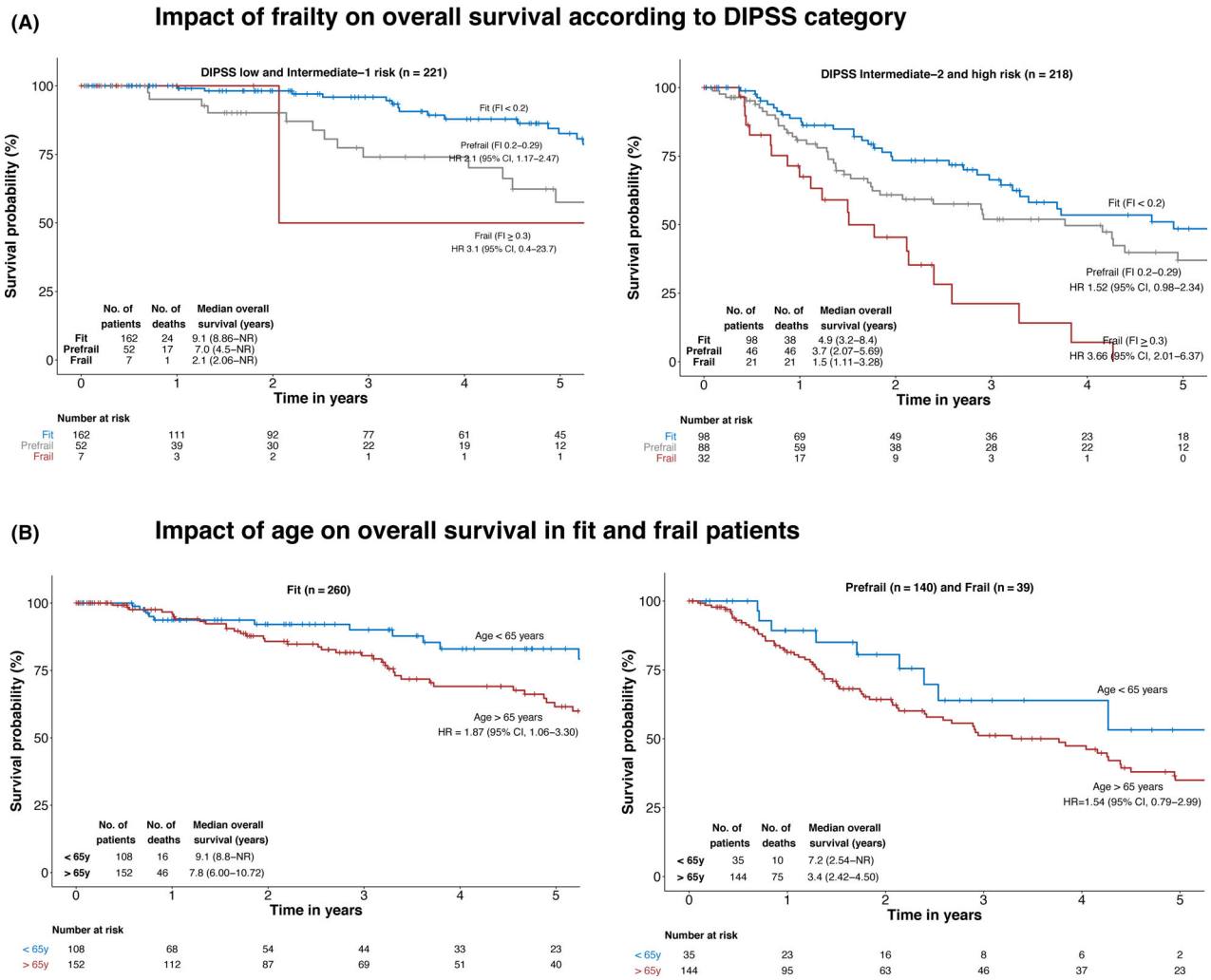

Fig 2. Impact of frailty on overall survival, stratified by DIPSS-risk and age in myelofibrosis. (A) Overall survival data, from time of first visit, among 221 patients with DIPSS low- and intermediate-risk myelofibrosis (left panel) and 218 patients with high-risk (right panel) myelofibrosis stratified by the frailty status defined using a 35-item cumulative deficit frailty index. (B) Overall survival data, from time of first visit, among 260 'fit' patients as per the frailty index (left panel) and 140 prefrail and 39 frail patients (right panel) stratified by age. For all estimates, $P \leq 0{\cdot}05$ was considered statistically significant. DIPSS, Dynamic International Prognostic Scoring system; Int, intermediate; CI, confidence interval; FI, frailty index. [Colour figure can be viewed at wileyonlinelibrary.com]

for treatment failure are presented in Figure S6. In multivariable analysis (Fig 4B) for treatment failure, the HR for frailty was 2·7 (95% CI, 1·3–5·6, $P = 0{\cdot}006$) and for prefrailty 1·6 (95% CI, 1·07–2·5, $P = 0{\cdot}02$). The other significant predictors for earlier treatment failure were a higher DIPSS score and transfusion dependence.

Association of frailty with driver and high-risk molecular mutations

Clonal haematopoiesis, specifically *JAK2* mutations in myelofibrosis, promote chronic inflammation that could accelerate loss of physiological reserve. In an exploratory analysis, we measured the difference in the frailty indices according to molecular mutations in patients with myelofibrosis. Among the MPN driver mutations, patients with the *JAK2* V617F mutation had higher frailty indices than those with *CALR*, *MPL* or neither of them (triple negative) ($P = 0{\cdot}003$, two-way ANOVA) (Fig 5). The pair-wise comparison showed that patients with the *JAK2* V617 mutation had a higher frailty index than patients with *CALR* ($P = 0{\cdot}001$, *t*-test) and MPL ($P = 0{\cdot}01$, *t*-test) and no difference was found when compared to triple negative patients. A total of 199 patients had information on other myeloid malignancy mutations, using a 49-gene NGS panel, which included the known high-risk molecular mutations such as *ASXL1*, *EZH2*, *SRSF2*, or *IDH1/IDH2*[32]. There was no difference in frailty indices between those with (1 or ≥ 2) or without high risk mutations ($P = 0{\cdot}096$, two-way ANOVA) (Fig 5).

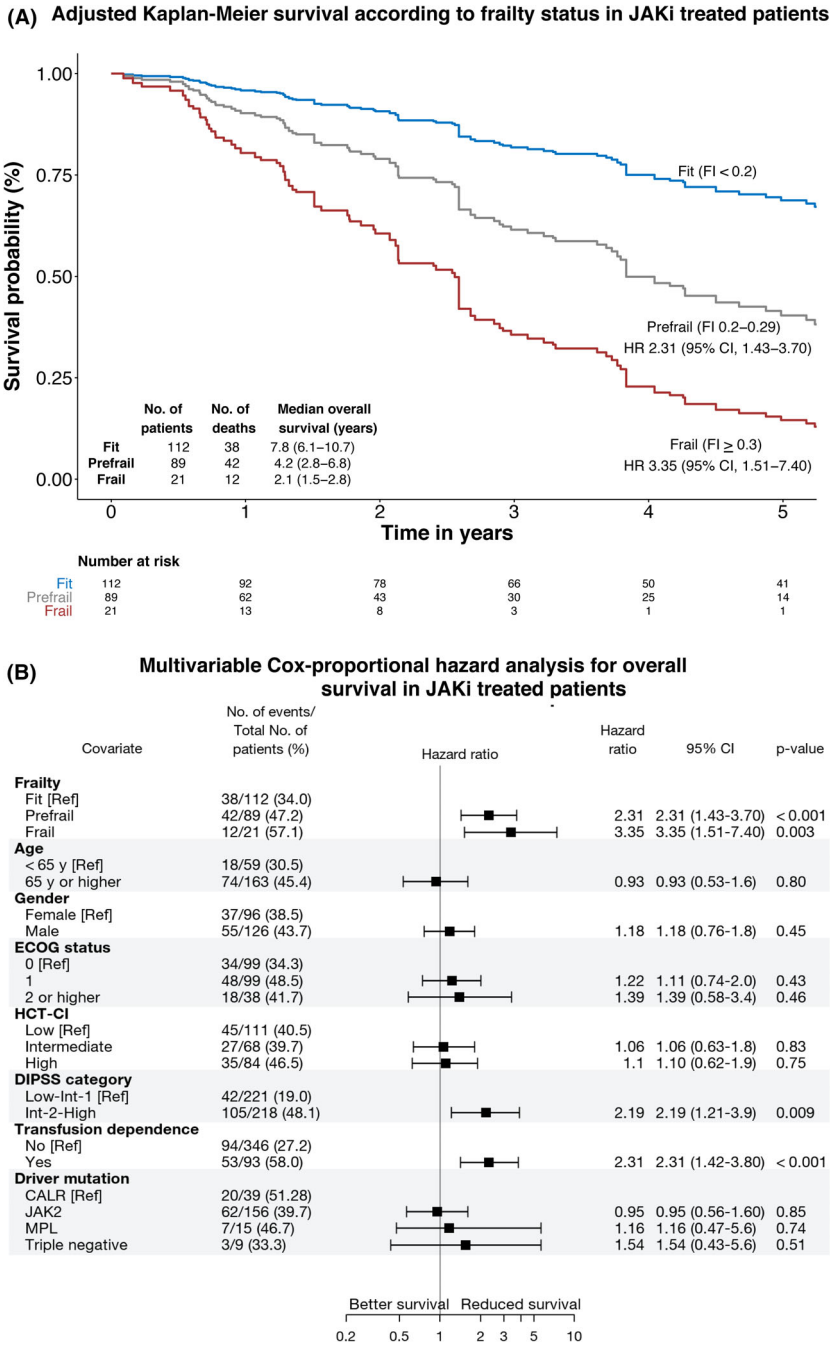

Fig 3. Overall survival in JAK inhibitor-treated patients with myelofibrosis according to frailty status. (A) Overall survival data, from time of starting JAK inhibitor treatment, among 222 patients with myelofibrosis, stratified by the frailty status defined by a 35-item cumulative deficit frailty index. The Kaplan–Meier curves shown were adjusted for the multivariable cox proportional regression model in (B). (B) Forest plot represents the HRs from the multivariable cox regression analysis for association between frailty status and overall survival in JAK inhibitor-treated patients. For all estimates, $P \leq 0{\cdot}05$ was considered statistically significant. ECOG, Eastern Co-operative Group scale; HCT-CI, haematopoietic stem cell transplant comorbidity index; DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; CI, confidence interval; FI, frailty index. [Colour figure can be viewed at wileyonlinelibrary.com]

Discussion

These results show the superior predictive ability of assessing frailty, compared to standalone measures of patient fitness such as age, comorbidity index and performance scores for overall survival and JAKi failure in patients with chronic phase myelofibrosis.

Our findings complement and extend the prior work on prognostication of key clinical outcomes in myelofibrosis. The chronological age is an important marker of patient

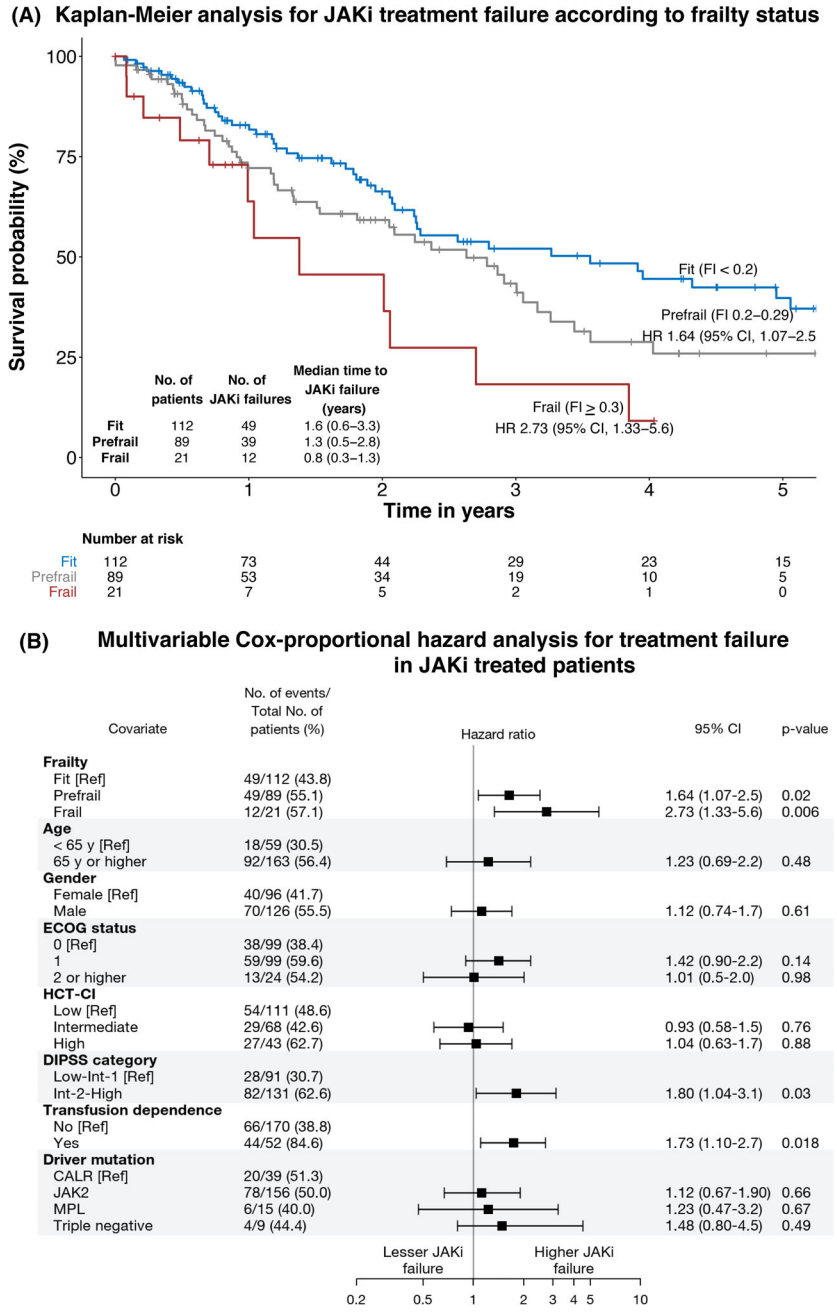

Fig 4. Impact of frailty on JAK inhibitor treatment failure in patients with myelofibrosis. (A) Treatment failure data (defined as per Canadian consensus criteria[26]) from time of starting JAK inhibitor treatment among 222 patients with myelofibrosis, according to frailty status, defined by a 35-item cumulative deficit frailty index. (B) Forest plot represents the HRs from the multivariable cox regression analysis for association between frailty status and treatment failure in JAK inhibitor-treated patients. For all estimates, $P \leq 0{\cdot}05$ was considered statistically significant. ECOG, Eastern Co-operative Group scale; HCT-CI, haematopoietic stem cell transplant comorbidity index; DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; CI, confidence interval; FI, frailty index. [Colour figure can be viewed at wileyonlinelibrary.com]

characteristics in widely used prognostic scores—IPSS,[17] DIPSS,[18] and DIPSS-plus.[19] In our multivariable model, we did not find an association between advanced age and inferior survival. There was also no difference between survival probabilities of younger and older patients once they had higher frailty. These results suggest that frailty assessment is a more important prognostic marker than advanced age for identifying patients with MF who are vulnerable to adverse outcomes. Other measures of fitness such as ECOG performance scale and the HCT-CI comorbidity index were not associated with overall survival, contrary to findings from other studies.[33,34] Both HCT-CI and ECOG are

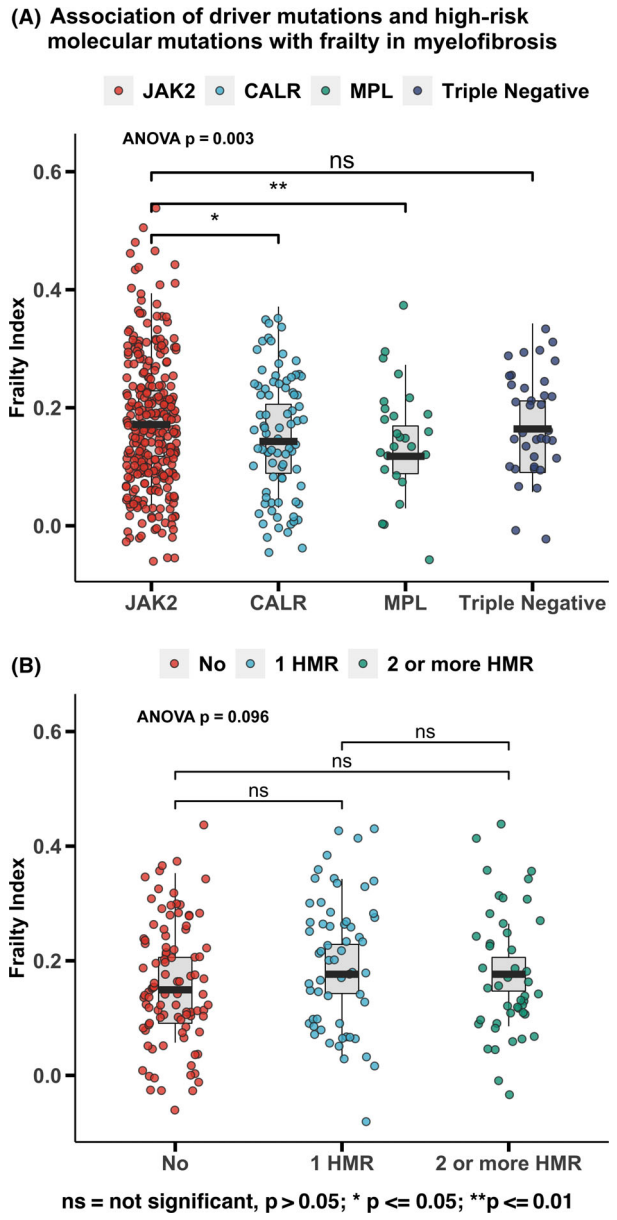

Fig 5. Association of driver mutations and high-risk molecular mutations with frailty in myelofibrosis. The scatter plots show the association of driver molecular mutations (n = 432) (A) and high-risk molecular mutations (n = 199) (B) with the frailty indices. The difference in mean frailty index was compared using two-way ANOVA, and pair-wise comparison was done with student t-tests. For all estimates, $P \leq 0{\cdot}05$ was considered statistically significant. [Colour figure can be viewed at wileyonlinelibrary.com]

unidimensional scales which measure comorbidities and performance, respectively, and do not necessarily indicate functional reserve. Furthermore, higher frailty also predicted at-risk individuals among those with DIPSS low- and intermediate-1 risk as well as DIPSS intermediate-2 and high-risk, confirming the additional discriminative ability in patients who were usually considered low-risk or high-risk by the present prognostic scoring systems.

Previous work has shown that higher DIPSS score, transfusion dependency, and the type of mutations (*ASXL1/EZH2*) are associated with a shorter time to JAKi therapy failure in MF.[28,35] We confirm these findings, furthermore showing that frailty rather than chronological age is important for predicting earlier treatment failure. It is recognised that the real-world JAK inhibitor treatment failure rates are higher[36] than those in controlled trials.[37] An argument that under-recruitment of older patients in clinical trials[38] could explain this discordancy may not hold true, because a post-hoc analysis of a COMFORT-I trial evaluating the JAKi drug ruxolitinib[39] has shown that advanced age does not impact JAKi treatment response rates. Our finding of an association of higher frailty with earlier JAKi therapy failure, therefore, raises a concern that 'frail' patients may have been under-represented in clinical trials and could explain the disparity in JAKi treatment outcomes in real-world and controlled settings. At the moment, there is no formal geriatric assessment before the clinical trial enrolment. As an increasingly higher number of patients with myelofibrosis are now treated on clinical trials with potential for adverse events, our study suggests that frailty would be a better variable for randomisation strata than age or performance status. Knowledge of frailty can also help in guiding the discussions about treatment outcomes and patient expectations. In addition, identification of non-oncological problems can inform potential interventions focused on decreasing the impact of these vulnerabilities.

Our exploratory analysis shows the clinical implication of a JAK2 mutation on the presence of frailty in patients with MF. Chronic, low-grade inflammation has been associated with accelerated ageing, age-related diseases, tissue dysfunction and frailty.[40,41] It is postulated that the proinflammatory cytokines and chemokines such as that induced by a JAK-STAT pathway produces cellular senescence.[42] Preclinical research has shown that JAK inhibition may alleviate the cellular senescence and delay frailty in old age.[43] Thus, a prospective clinical study will be needed to assess whether JAKi therapy could prevent or delay frailty in patients with myelofibrosis who are fit or prefrail.

With regard to frailty measurement, frailty indices similar to ours measure the heterogeneity in the fitness levels during ageing as an accumulation of health deficits, evaluate impairments in many biological systems,[44] are graded,[24] are conceptually simple[24] and can be constructed for use with retrospective data that did not specifically measure frailty. In the oncology setting, frailty is more common (13–43% in solid[7] and 42% in haematological[45] cancers) compared to community-dwelling adults (10% in those aged 65–75 years, 40% in those > 80 years[46,47]). In our study, we found a similar prevalence, but the prevalence of frailty could have been higher had we restricted our cohort to older individuals, and obtained data on all dimensions of the frailty index prospectively. Indeed, one of the limitations of our study is the retrospective collection of data on three dimensions of frailty—physical function, polypharmacy, and social isolation.

In addition, the frailty measurement in our analyses did not include objective physical performance measures such as hand grip strength and gait speed. Recent studies have shown that frailty scores which contain one or two physical performance measures may have better predictive ability than those without.[48]

In conclusion, our study highlights the prognostic value of measuring frailty in patients with myelofibrosis in predicting the adverse clinical outcomes. We recommend inclusion of the frailty measurement in clinical trial designs. Future directions include implementing novel measures to reduce or prevent frailty for improving adverse clinical outcomes in patients with myelofibrosis.

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The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

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Author contributions

Dr Gupta had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bankar, Gupta. Acquisition, analysis, or interpretation of data: Bankar, Xu, Yang, Alibhai. Drafting of the manuscript: Bankar, Gupta. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Bankar, Xu, Yang. Obtained funding: Gupta. Administrative, technical, or material support: Bankar, Alibhai, Gupta, Arruda, Claudio, Malik, Cheung, Siddiq. Study supervision: Gupta, Alibhai.

Conflict of interest

VG received an honorarium, clinical trial funding through an institution and served on an advisory board of Novartis, BMS-Celgene, Abb Vie, Pfizer and Sierra Oncology.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. 35-item frailty index.

Fig S1. Prevalence of frailty index deficits in the study population.

Fig S2. Univariate Kaplan–Meier analysis for overall survival.

Fig S3. Univariate competing risk analysis for leukaemic transformation.

Fig S4. Calibration plot for internal validation of multivariable Cox-proportional hazards model using boot strapping.

Fig S5. Univariate Kaplan–Meier analysis for overall survival in patients treated with JAK inhibitors.

Fig S6. Univariate Kaplan–Meier analysis for treatment failure in JAK inhibitor-treated patients.

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