Original Article

Frailty status and risk of hypoglycemia-requiring hospital care among older adults with type 2 diabetes in Sulawesi, Indonesia: A retrospective cohort study

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Abstract

Frailty is a state of increased vulnerability to adverse outcomes and is associated with poor health and increased mortality among older adults with type 2 diabetes mellitus (T2DM). The aim of this study was to assess the association between frailty status and hypoglycemia-related emergency department visits or hospitalizations among older adults with T2DM. A multicenter retrospective cohort study was performed using medical records from 10 hospitals in five provinces of Sulawesi, Indonesia (Gorontalo, South Sulawesi, North Sulawesi, Central Sulawesi, and Southeast Sulawesi), from January 2021 to December 2025. The study included 2,847 patients with T2DM aged ≥60 years. Frailty was evaluated using the fatigue, resistance, ambulation, illness, and weight loss (FRAIL) scale and categorized as robust, pre-frail, or frail. The primary outcome was time to a hypoglycemia-related emergency department visit or unplanned hospital admission. Multivariable Cox proportional hazards regression was used to estimate adjusted hazard ratios (aHRs). The cohort had a mean age of 71.4±6.8 years and 58.3% were female; frailty was identified in 31.2% and pre-frailty in 34.6%. There were 387 hypoglycemia-related events during a median follow-up of 3.2 years. Compared with robust participants, frail participants had a higher hazard of the primary outcome (aHR: 2.74; 95% confidence interval (CI): 2.08–3.61; $p<0.001$), as did pre-frail participants (aHR: 1.58; 95%CI: 1.18–2.12; $p=0.002$). Frailty was independently associated with an increased risk of hypoglycemia requiring hospital care among older adults with T2DM. Frailty status may act as an important clinical indicator for identifying vulnerable patients, with a potential to optimize individualized diabetes management. Further multicenter research beyond Sulawesi is warranted to establish broader applicability across Indonesia.

Keywords: Frailty, hypoglycemia, hospitalization, type 2 diabetes mellitus, older adults

Introduction

There has been a considerable increase in the global prevalence of type 2 diabetes mellitus (T2DM) among adults, particularly older adults, due to population aging and lifestyle changes [1]. According to the International Diabetes Federation (IDF), approximately 589 million adults aged 20–79 years (11.1%) were living with diabetes worldwide in 2024, with this number projected to reach 853 million by 2050. The burden is particularly pronounced in older populations, with diabetes prevalence reaching 23.7% among adults older than 65 years and 24.8% among those aged 75–79 years [2]. In Indonesia, approximately 20.4 million adults were living with diabetes in 2024, representing a national prevalence of 11.3%, highlighting the substantial healthcare

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Received: July 2, 2026 - Revised: October 18, 2026 - Accepted: October 30, 2026 - Published online: November 4, 2026

burden associated with this condition [3]. These epidemiological trends underscore the growing need for individualized diabetes management in older adults, whose heterogeneous clinical characteristics, multiple comorbidities, declining functional capacity, and reduced physiological reserve may increase vulnerability to treatment-related complications, including hypoglycemia requiring hospital care [1,4-6].

Hypoglycemia is one of the most serious acute complications in older adults with T2DM and may lead to emergency department visits, hospitalizations, falls, fractures, cardiovascular events, cognitive decline, and mortality [4,5]. Older adults are at increased risk because of impaired counter-regulation, reduced renal clearance of glucose-lowering drugs, irregular dietary intake, and polypharmacy [6,7]. Severe hypoglycemia in older adults with diabetes is a serious, potentially life-threatening event associated with emergency healthcare utilization and adverse outcomes, including falls, cardiovascular events, cognitive decline, and increased mortality [8,9]. These consequences highlight the importance of identifying factors that may increase susceptibility to severe hypoglycemia, particularly frailty.

Frailty is a clinical syndrome characterized by reduced physiological reserve and increased vulnerability to stressors due to cumulative declines across multiple physiological systems, and has been recognized as an important predictor of adverse health outcomes in older adults with diabetes [10]. This syndrome involves physical, cognitive, and social domains and is significantly associated with disability, hospitalization, and mortality [11]. Although limited quantitative data exist on frailty in older adults with T2DM, the estimated prevalence is suggested to be considerably higher than that observed in the general older adult population, ranging from approximately one-quarter to nearly half of the studied population, depending on the case ascertainment method and the characteristics of the study population examined [12].

Frailty can be both a consequence and a cause of hypoglycemia. Frailty, on the one hand, predisposes to hypoglycemia through sarcopenia-mediated reduction in hepatic glycogen stores, decreased appetite and caloric intake, impaired renal drug clearance, and cognitive deficits that impact self-management capacity [12]. In contrast, recurrent hypoglycemia has been shown to increase morbidity and mortality and deteriorate physical performance and cognition, all of which are components of frailty status [13]. This vicious cycle has been defined as a major driving force for negative results in diabetes care among older patients [14].

Although frailty-informed diabetes care has received increasing attention, its implementation across diverse populations remains limited, particularly in low- and middle-income countries where access to comprehensive geriatric assessment and integrated care may be constrained [15]. In Indonesia, population aging has increased the importance of addressing frailty and its associated clinical complications among older adults with T2DM [16]. However, evidence specifically examining the association between frailty and hypoglycemia requiring hospital care in this population remains insufficient. Much of the existing evidence has been generated outside Southeast Asia, and its applicability to Indonesian healthcare settings may be influenced by differences in nutritional practices, healthcare delivery, medication access, and broader socioeconomic conditions [15,17]. To address this contextual evidence gap, the present study examines the association between frailty status and hypoglycemia requiring hospital care using multicenter hospital data from five provinces in Sulawesi, Indonesia. These findings provide regionally relevant evidence without implying national representativeness.

Methods

Study design and setting

This was a multicenter retrospective cohort study using electronic medical records and hospital administrative databases from 10 tertiary and secondary referral hospitals across five provinces in Sulawesi, Indonesia: Gorontalo (two hospitals), South Sulawesi (three hospitals), North Sulawesi (one hospital), Central Sulawesi (two hospitals), and Southeast Sulawesi (two hospitals). The study timeframe was from January 1, 2021, to December 31, 2025. The participating sites included urban and more rural referral settings and were selected to provide variation in healthcare infrastructure within the study region.

Study population and eligibility criteria

Eligible participants were adults aged ≥60 years with a physician-confirmed diagnosis of T2DM (ICD-10 code: E11.x) recorded in the medical records for a minimum of 12 months before the index date. The index date was the date of the first frailty assessment during the study period. Patients needed to have at least one outpatient or hospitalization record in the 12 months before the index date and at least 6 months of observable follow-up. The age threshold of ≥60 years was applied consistently throughout database extraction, cohort definition, subgroup analysis, and reporting. The exclusion criteria were type 1 diabetes mellitus or secondary diabetes; active malignancy or chemotherapy during the study period; end-stage renal disease requiring dialysis; severe hepatic insufficiency (Child-Pugh class C); missing data on frailty assessment; and hospice or palliative care enrollment at baseline. A total of 3,412 patient records, with details presented in **Table 1**, were screened. After application of the prespecified eligibility and exclusion criteria, 2,847 participants were included in the final analytical cohort (**Figure 1**).

Table 1. Distribution of participants by hospital and province

Province	Hospital	Type	n	%
Gorontalo	Prof. Dr. H. Aloei Saboe Regional Hospital	Tertiary	312	11.0
	Otanaha Regional Hospital	Secondary	198	7.0
South Sulawesi	Dr. Wahidin Sudirohusodo General Hospital	Tertiary	487	17.1
	Labuang Baji Regional Hospital	Secondary	289	10.1
	Makassar Hajj Regional Hospital	Secondary	241	8.5
North Sulawesi	Prof. Dr. RD Kandou General Hospital	Tertiary	378	13.3
Central Sulawesi	Undata Regional Hospital	Tertiary	274	9.6
	Madani Regional Hospital	Secondary	196	6.9
Southeast Sulawesi	Bahteramas Regional Hospital	Tertiary	268	9.4
	Kendari Municipality Regional Hospital	Secondary	204	7.2
Total			2,847	100

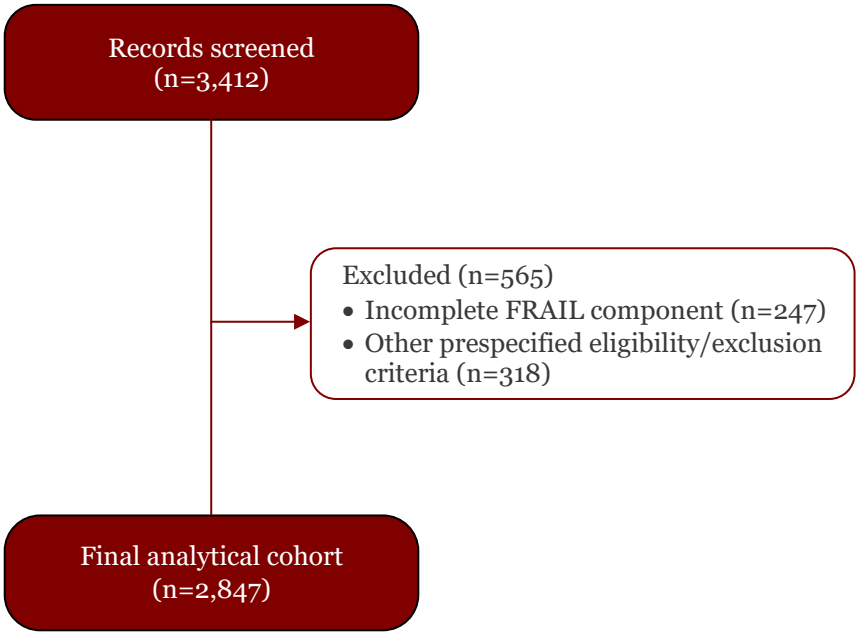


Figure 1. Flowchart of participant screening, exclusions, and final analytical cohort. FRAIL: fatigue, resistance, ambulation, illness, and weight loss.

Follow-up time and censoring rules

Follow-up time was calculated from the index date to the earliest of the following: (1) first hypoglycemia-related emergency department visit or unplanned hospital admission (event); (2) death from any cause (competing event); (3) transfer to a non-participating facility; (4) last recorded clinical encounter for patients with no subsequent visits for >12 months (loss to follow-up); or (5) administrative end of study (December 31, 2025). Patients were censored at the date

of the applicable censoring event. Because eligibility required at least 6 months of observable follow-up, patients without sufficient follow-up after the index date were not included in the analytic cohort.

Frailty assessment

The fatigue, resistance, ambulation, illness, and weight loss (FRAIL) scale is a five-item screening instrument assessing fatigue, resistance, ambulation, illness (≥5 comorbidities), and weight loss (>5% within one year). Total scores range from 0 to 5, categorizing participants as robust (0), pre-frail (1–2), or frail (3–5). The scale was selected for its brevity and feasibility for routine clinical use. In an Indonesian validation study involving 101 older adults, the Indonesian version (Ina-FRAIL) demonstrated a Cronbach's alpha of 0.530, indicating limited internal consistency, and a test–retest kappa coefficient of 0.951 [18]. These reliability estimates were obtained from the published validation study rather than the present retrospective cohort.

Operationalization of frailty from medical records

The FRAIL scale was selected for this study based on several scientific considerations. First, frailty is recognized as a clinical syndrome characterized by reduced physiological reserve and increased vulnerability to stressors, involving physical, cognitive, and social domains, and is significantly associated with disability, hospitalization, and mortality in older adults with diabetes. Second, the instrument's five binary items can be systematically operationalized from retrospective medical records—Fatigue from documented complaints, Resistance and Ambulation from functional-status or physiotherapy assessments, Illness from active diagnoses, and Weight Loss from serial weight measurements—thereby enabling standardized ascertainment in a retrospective multicenter design. Third, the quality of retrospective FRAIL classification was empirically verified in this study through independent re-extraction of approximately 10% of records (n=300), yielding a Cohen's kappa of 0.84 (95% confidence interval (CI): 0.79–0.89), indicating excellent inter-rater agreement. Fourth, the instrument's brevity and categorical output facilitate integration into routine clinical workflows, which is particularly relevant in low- and middle-income settings where access to comprehensive geriatric assessment may be constrained. Fifth, the estimated prevalence of frailty in older adults with T2DM is considerably higher than in the general older population, underscoring the clinical importance of employing a validated, feasible screening tool in this high-risk group. Finally, to address potential misclassification from incomplete data, participants with missing FRAIL components were excluded from the primary complete-case analysis, and multiple imputation by chained equations (MICE) with 20 imputed datasets was performed as a sensitivity analysis.

Handling of missing data and quality assurance

All participating hospitals used structured clinical documentation to record functional status, body weight, and comorbidities. A total of 3,094 participants satisfied all non-frailty eligibility criteria, had an independently ascertainable index date, and possessed valid follow-up information. Of these, 247 participants (8.0%) had incomplete information on at least one of the five FRAIL components and were excluded from the primary complete-case analysis. The remaining 2,847 participants (92.0%) had complete FRAIL assessments and constituted the primary analytical cohort.

MICE was performed as a sensitivity analysis involving all 3,094 otherwise eligible participants, including 2,847 participants with complete FRAIL assessments and 247 participants with incomplete FRAIL information. The index date was defined as the first qualifying clinical encounter during the study period, independently of FRAIL data completeness. The same encounter-based algorithm was applied to all participants, and only clinical information available on or before the index date was used to determine baseline FRAIL status.

Missing values in the five binary FRAIL components (fatigue, resistance, ambulation, illness, and weight loss) were imputed using chained equations with binary logistic regression and 20 imputed datasets. The imputation model included baseline demographic characteristics, diabetes-related clinical variables, medication exposure, comorbidities, hospital or study location, event status, and the Nelson–Aalen cumulative baseline hazard estimate. Observed FRAIL component values were retained without modification.

Within each imputed dataset, the five FRAIL component scores were summed, and participants were classified according to the predefined frailty categories. The fully adjusted Cox proportional hazards regression model was fitted separately to each imputed dataset, and regression coefficients and standard errors were combined using Rubin's rules. A total of 300 medical records (approximately 10% of the cohort) were independently re-extracted by a second reviewer. Inter-rater agreement for the overall frailty classification showed a Cohen's kappa of 0.84 (95%CI: 0.79–0.89), indicating excellent agreement.

Primary outcome

The primary outcome was time to the first hypoglycemia-related emergency department visit or unplanned hospital admission caused by hypoglycemia as the principal reason for the encounter. An event was captured when both a clinical criterion and an administrative criterion were met.

Clinical criterion: A documented capillary or venous blood glucose level <70 mg/dL (3.9 mmol/L) at emergency department triage or pre-hospital assessment, with treatment for acute hypoglycemia documented in the encounter record. Intravenous dextrose was recorded when administered but was not treated as the sole defining feature of the event.

Administrative criterion: A primary (first-listed) discharge or encounter diagnosis corresponding to hypoglycemia. The analytic extraction used the following standardized diagnostic labels: E11.649 (T2DM with hypoglycemia without coma), E16.0 (drug-induced hypoglycemia without coma), E16.1 (other hypoglycemia), and E16.2 (hypoglycemia, unspecified). Because E11.649 is an ICD-10-CM-specific label, the local hospital coding system and the exact mapping used to generate this analytic label should be documented in the study's coding dictionary/supplementary materials before final submission.

To ensure that the outcome reflected clinically relevant acute hypoglycemia rather than incidental hypoglycemia during an encounter for another condition, only events in which hypoglycemia was the primary reason for the emergency department visit or hospital admission were included. Hypoglycemia recorded only as a secondary diagnosis during an admission initiated for another condition (e.g., pneumonia or elective surgery) was excluded. Emergency department records were reviewed to confirm that hypoglycemia prompted the visit, and in-hospital hypoglycemia developing after admission for another diagnosis was not counted. All outcome events were independently verified by two trained physician reviewers using emergency department triage notes, admission records, and discharge summaries; discrepancies were resolved by consensus with a third reviewer.

Covariates

Baseline covariates were prespecified based on prior clinical evidence and a directed acyclic graph (DAG)-informed causal framework identifying plausible confounders of the frailty–hypoglycemia association. Covariates extracted from medical records included demographic variables (age, sex, province, and body mass index (BMI)); diabetes-related variables (diabetes duration, HbA1c, fasting blood glucose, and use of insulin, sulfonylurea, metformin, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists); comorbidities (hypertension, chronic kidney disease (CKD) stages 3–4, coronary artery disease, cerebrovascular disease, heart failure, depression, and cognitive impairment); polypharmacy (≥5 concurrent medications); and prior hypoglycemic episodes within 12 months before the index date. No data-driven variable selection procedures (e.g., stepwise regression) were applied; all covariates were retained in the models regardless of statistical significance to preserve the prespecified causal structure and minimize the risk of collider or overadjustment bias.

Statistical analysis

Baseline characteristics were expressed as mean ± standard deviation (SD) for continuous variables and frequencies with percentages for categorical variables. Differences across frailty groups (robust, pre-frail, and frail) were assessed using one-way analysis of variance (ANOVA) and post-hoc Bonferroni correction for continuous variables or chi-square tests for categorical variables.

Kaplan–Meier methods were used to describe hypoglycemia-free survival, and differences between frailty groups were compared using the log-rank test. Because death was a competing

event, Kaplan–Meier estimates were interpreted as cause-specific survival rather than as cumulative incidence probabilities. Adjusted hazard ratios (aHRs) with 95%CIs were estimated using multivariable Cox proportional hazards regression. Model 1 was adjusted for age and sex. Model 2 additionally controlled for diabetes duration, HbA1c, BMI, CKD, insulin use, and sulfonylurea use. Model 3 additionally included polypharmacy, prior hypoglycemic episodes, depression, cognitive impairment, and province. Schoenfeld residuals were used to assess the proportional hazards assumption.

Sensitivity analyses were performed by limiting the outcome to clinically significant hypoglycemia (Level 2; blood glucose <54 mg/dL (3.0 mmol/L)), as defined by the International Hypoglycemia Study Group classification and the American Diabetes Association Standards of Care, and by excluding participants with CKD stages 3–4. Additional stratified analyses were performed according to insulin use and province [19,20]. A Fine–Gray subdistribution hazard model was used to account for death as a competing event. Hospital-level clustering was not separately modeled; therefore, the confidence intervals may not fully account for within-hospital correlation in documentation, prescribing, admission, and coding practices. Statistical significance was defined as a two-sided *p*-value <0.05. All analyses were performed using Stata version 17.0 (StataCorp, College Station, TX, USA).

Results

Participant characteristics and frailty status

In total, 2,847 adults aged ≥60 years with T2DM were included from 10 hospitals across five provinces in Sulawesi, Indonesia: Gorontalo (two hospitals), South Sulawesi (three hospitals), North Sulawesi (one hospital), Central Sulawesi (two hospitals), and Southeast Sulawesi (two hospitals) (mean age: 71.4±6.8 years; 58.3% female). According to the FRAIL scale, 974 (34.2%) were robust, 985 (34.6%) were pre-frail, and 888 (31.2%) were frail. Robust participants were generally younger, had a shorter diabetes duration, higher BMI, and lower prevalence of CKD, depression, cognitive impairment, and polypharmacy than frail participants (all $p<0.001$). Baseline characteristics are presented in **Table 2**.

Table 2. Baseline characteristics of study participants by frailty status

Variable	Robust (n=974)	Pre-frail (n=985)	Frail (n=888)	*p*-value
Age, years (mean±SD)	68.2±5.4	71.5±6.2	75.1±7.3	<0.001[a]
Female, n (%)	538 (55.2)	576 (58.5)	546 (61.5)	0.021[b]
BMI, kg/m² (mean±SD)	25.8±3.9	24.3±4.1	22.1±3.7	<0.001[a]
Diabetes duration, years (mean±SD)	8.4±5.1	11.2±6.3	14.7±7.2	<0.001[a]
HbA1c, % (mean±SD)	7.4±1.2	7.6±1.4	7.2±1.6	<0.001[a]
Fasting blood glucose, mg/dL (mean±SD)	142.3±38.5	148.7±42.1	136.8±45.3	<0.001[a]
Insulin use, n (%)	287 (29.5)	394 (40.0)	512 (57.7)	<0.001[b]
Sulfonylurea use, n (%)	341 (35.0)	378 (38.4)	402 (45.3)	<0.001[b]
Metformin use, n (%)	682 (70.0)	641 (65.1)	478 (53.8)	<0.001[b]
DPP-4 inhibitor use, n (%)	198 (20.3)	187 (19.0)	142 (16.0)	0.048[b]
CKD stages 3–4, n (%)	112 (11.5)	189 (19.2)	278 (31.3)	<0.001[b]
Hypertension, n (%)	524 (53.8)	587 (59.6)	589 (66.3)	<0.001[b]
Coronary artery disease, n (%)	98 (10.1)	142 (14.4)	178 (20.0)	<0.001[b]
Depression, n (%)	62 (6.4)	108 (11.0)	187 (21.1)	<0.001[b]
Cognitive impairment, n (%)	48 (4.9)	97 (9.8)	203 (22.9)	<0.001[b]
Polypharmacy (≥5 medications), n (%)	312 (32.0)	478 (48.5)	589 (66.3)	<0.001[b]
Prior hypoglycemic episode, n (%)	78 (8.0)	134 (13.6)	224 (25.2)	<0.001[b]

[a] Analyzed using one-way analysis of variance (ANOVA)
[b] Analyzed using chi-square test

Incidence of hypoglycemia-related hospital care

During a median follow-up of 3.2 years (interquartile range (IQR): 2.1–4.1 years; total 8,214 person-years), a total of 387 hypoglycemia-related emergency department visits or unplanned hospital admissions were observed, with an overall incidence rate of 4.71 per 100 person-years (**Table 3**). The incidence rate was higher among frail participants (9.20 per 100 person-years) than among pre-frail (4.23 per 100 person-years) and robust participants (1.87 per 100 person-

years) (**Table 3**). Kaplan–Meier hypoglycemia-free survival curves showed clear separation between frailty groups (log-rank $p<0.001$; **Figure 2**).

Table 3. Incidence rates of hypoglycemia-related emergency department visits or hospitalizations by frailty status

Frailty status	Events (n)	Person-years	Incidence rate (per 100 PY)	95%CI
Robust	56	2,994	1.87	1.44–2.43
Pre-frail	127	3,002	4.23	3.55–5.03
Frail	204	2,218	9.20	8.01–10.56
Overall	387	8,214	4.71	4.27–5.20

Incidence rates were calculated as events per 100 person-years (PY).

Association between frailty and hypoglycemia-related hospital Care

In the fully adjusted model (Model 3), frailty remained independently associated with a higher hazard of the primary outcome (aHR: 2.74; 95%CI: 2.08–3.61; $p<0.001$) compared with robust status. Pre-frailty was also associated with a higher hazard (aHR: 1.58; 95%CI: 1.18–2.12; $p=0.002$). Other independent predictors included insulin use (aHR: 1.89; 95%CI: 1.52–2.35), CKD stages 3–4 (aHR: 1.64; 95%CI: 1.29–2.08), prior hypoglycemic episode (aHR: 2.12; 95%CI: 1.68–2.67), and cognitive impairment (aHR: 1.47; 95%CI: 1.12–1.93). The results are presented in **Table 4**.

Sensitivity and subgroup analyses

Similar findings were observed in sensitivity analyses restricted to severe hypoglycemia (<54 mg/dL; frail vs. robust: aHR 3.12; 95%CI: 2.14–4.55) and after excluding participants with CKD stages 3–4 (aHR: 2.58; 95%CI: 1.87–3.56). In stratified analyses by insulin use, the frailty–hypoglycemia association was present among insulin users (aHR: 2.41; 95%CI: 1.72–3.38) and non-insulin users (aHR: 2.93; 95%CI: 1.84–4.67), with no statistical evidence of interaction ($p=0.384$). Estimates were also similar across provinces (**Table 5**).

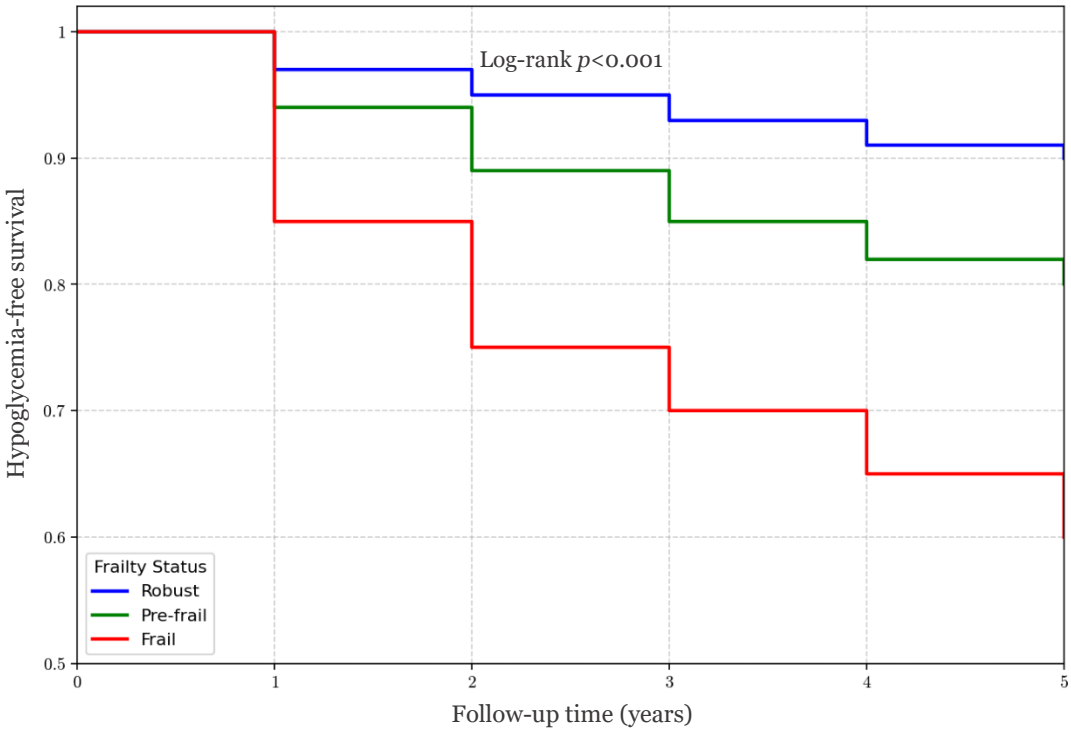


Figure 2. Kaplan–Meier hypoglycemia-free survival curves by frailty status.

In the longitudinal analysis of 8,214 person-years, frailty status was strongly associated with the primary outcome. Incidence rates increased from 1.87 per 100 person-years in the robust group to 4.23 in the pre-frail group and 9.20 in the frail group (log-rank $p<0.001$).

Table 4. Multivariable Cox proportional hazards regression analysis of factors associated with hypoglycemia requiring hospital care among older adults with T2DM

Variable	Crude HR (95%CI)	Model 1 aHR (95%CI)	Model 2 aHR (95%CI)	Model 3 aHR (95%CI)
Frailty status (ref: Robust)				
Pre-frail	2.18 (1.62–2.93)***	1.82 (1.34–2.47)**	1.67 (1.23–2.27)**	1.58 (1.18–2.12)**
Frail	4.87 (3.69–6.43)***	3.48 (2.62–4.63)***	3.01 (2.26–4.01)***	2.74 (2.08–3.61)***
Age (per year)	1.06 (1.04–1.08)***	1.04 (1.02–1.06)***	1.03 (1.01–1.05)**	1.02 (1.00–1.04)*
Female sex	1.14 (0.93–1.40)	1.08 (0.87–1.34)	1.05 (0.85–1.30)	1.03 (0.83–1.28)
Diabetes duration (per year)	1.05 (1.03–1.07)***		1.03 (1.01–1.05)**	1.02 (1.00–1.04)*
Insulin use	2.41 (1.97–2.95)***		1.98 (1.59–2.46)***	1.89 (1.52–2.35)***
Sulfonylurea use	1.58 (1.29–1.94)***		1.42 (1.14–1.77)**	1.34 (1.07–1.68)*
HbA1c (per 1%)	0.88 (0.82–0.95)**		0.91 (0.84–0.99)*	0.92 (0.85–1.00)
CKD stages 3–4	2.18 (1.76–2.70)***		1.72 (1.36–2.17)***	1.64 (1.29–2.08)***
BMI (per kg/m²)	0.94 (0.91–0.97)***		0.96 (0.93–0.99)*	0.97 (0.94–1.00)
Prior hypoglycemic episode	3.12 (2.51–3.88)***			2.12 (1.68–2.67)***
Cognitive impairment	2.84 (2.24–3.60)***			1.47 (1.12–1.93)**
Polypharmacy	1.92 (1.57–2.35)***			1.28 (1.02–1.61)*
Depression	1.78 (1.38–2.29)***			1.19 (0.89–1.59)
Province (ref: South Sulawesi)				
North Sulawesi	1.18 (0.88–1.58)			1.12 (0.82–1.53)
Central Sulawesi	0.97 (0.70–1.34)			0.94 (0.67–1.32)
Southeast Sulawesi	1.14 (0.82–1.59)			1.08 (0.76–1.54)
Gorontalo	0.91 (0.60–1.38)			0.89 (0.58–1.37)

aHR: adjusted hazard ratio; BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; HbA1c: glycated hemoglobin
Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for diabetes duration, HbA1c, BMI, CKD stages 3–4, insulin use, and sulfonylurea use. Model 3 was further adjusted for polypharmacy, prior hypoglycemic episodes, depression, cognitive impairment, and province (categorical, with South Sulawesi as the reference category).
* Statistically significant at $p<0.05$
** Statistically significant at $p<0.01$
*** Statistically significant at $p<0.001$

After adjustment for measured baseline covariates, frail participants had a higher hazard of the primary outcome (aHR: 2.74; 95%CI: 2.08–3.61; p<0.001), while pre-frail participants had a higher hazard than robust participants (aHR: 1.58; 95%CI: 1.18–2.12; p=0.002). These associations remained in sensitivity analyses for severe hypoglycemia, exclusion of CKD stages 3–4, and stratification by insulin use.

Table 5. Subgroup analyses in estimating adjusted hazard ratios for frail versus robust participants

Subgroup	aHR (95%CI)	p-interaction
Insulin use		0.384
Yes	2.41 (1.72–3.38)	
No	2.93 (1.84–4.67)	
CKD status		0.512
CKD stages 3–4	2.48 (1.58–3.89)	
No CKD stages 3–4	2.58 (1.87–3.56)	
Province		0.673
Gorontalo	2.81 (1.74–4.54)	
South Sulawesi	2.69 (1.78–4.07)	
North Sulawesi	2.78 (1.62–4.77)	
Central Sulawesi	2.64 (1.48–4.71)	
Southeast Sulawesi	2.91 (1.39–6.09)	
Age group		0.298
60–74 years	2.56 (1.78–3.68)	
≥75 years	3.04 (2.08–4.44)	

aHR: adjusted hazard ratio; CI: confidence interval; CKD: chronic kidney disease
All models were fully adjusted (Model 3). Interaction p-values were obtained by including multiplicative interaction terms in the Cox models.

In the MICE sensitivity analysis, the pooled estimates remained statistically significant for both pre-frailty (aHR: 1.89; 95%CI: 1.42–2.52; p<0.001) and frailty (aHR: 3.68; 95%CI: 2.79–4.85; p<0.001), with robust status as the reference category (**Supplementary Table 1**). Although the estimates were higher than those obtained in the primary complete-case analysis (aHR: 1.58 for pre-frailty and 2.74 for frailty), the direction and statistical significance of the associations were consistent with the primary findings.

Competing risk analysis

A Fine–Gray subdistribution hazards model was applied with death treated as a competing event. Compared with robust participants, frail participants had a subdistribution hazard ratio (sHR) of 2.58 (95%CI: 1.94–3.43; p<0.001), while pre-frail participants had an sHR of 1.51 (95%CI: 1.12–2.04; p=0.007) (**Table 6**).

Table 6. Competing-risk analysis using the Fine–Gray model for the primary outcome

Variable	sHR (95%CI)	p-value
Frailty status (ref: Robust)		
Pre-frail	1.51 (1.12–2.04)	0.007
Frail	2.58 (1.94–3.43)	<0.001

CI: confidence interval; sHR: subdistribution hazard ratio
Model fully adjusted for all covariates in Model 3. Death from any cause was treated as a competing event.

Discussion

In the present multicenter retrospective cohort of 2,847 adults aged ≥60 years with T2DM from five provinces in Sulawesi, frailty was associated with a substantially higher hazard of hypoglycemia-requiring hospital care. Compared with robust participants, the adjusted hazard was 2.74-fold higher in frail participants and 1.58-fold higher in pre-frail participants. These estimates persisted after adjustment for measured baseline demographic, clinical, and pharmacological covariates and were directionally consistent in sensitivity analyses. These findings are in line with the previously published systematic review and meta-analysis suggesting an association between frailty and adverse clinical outcomes among older adults with diabetes, including hypoglycemia-related outcomes [21]. The point estimates observed in the present

cohort (aHR: 2.74 for frail; aHR: 1.58 for pre-frail) were statistically significant and may partly reflect the high prevalence of insulin use (57.7%), CKD stages 3–4 (31.3%), and polypharmacy (66.3%) among frail participants. However, direct comparison of effect estimates across studies should be interpreted cautiously given differences in study populations, outcome definitions, frailty ascertainment methods, and covariate adjustment strategies.

The frailty–hypoglycemia association may have several plausible biological and clinical explanations. Sarcopenia, reduced appetite, weight loss, impaired renal function, and cognitive impairment can coexist with frailty and may increase vulnerability to hypoglycemia [22-26]. In the present study, however, these mechanisms were not directly measured as mediators. Therefore, the observed associations should not be interpreted as evidence that any single mechanism caused the increased hazard. Cognitive impairment, as found in the present study, may further impair the capacity to recognize early hypoglycemic symptoms. Reduced or irregular food intake without corresponding dose adjustment of insulin or sulfonylurea therapy represents a particularly important proximal mechanism, as the glucose-lowering effect of these agents continues irrespective of caloric intake [27]. Limited caregiver support may also delay recognition and treatment of hypoglycemic episodes, increasing the likelihood that events progress to a severity requiring hospital care [27]. These behavioral pathways are consistent with the higher prevalence of polypharmacy (66.3%), insulin use (57.7%), and prior hypoglycemic episodes (25.2%) observed among frail participants in this cohort.

The association was observed across the five participating provinces and in both insulin and non-insulin users. However, the absence of statistically significant interaction should be interpreted as no statistical evidence of effect modification rather than proof that the association is identical across settings. Importantly, the cohort was drawn exclusively from 10 hospitals in five provinces of Sulawesi. The findings therefore provide evidence from a geographically varied multicenter setting within Sulawesi but do not establish national representativeness for Indonesia. The study also did not directly measure ethnicity, so no inference about ethnic homogeneity or ethnic effect modification can be made.

The lower HbA1c levels observed among frail participants should be interpreted cautiously in the context of previous research on glycemic control and adverse outcomes in older adults [28]. Intensive glycemic control has been associated with increased severe hypoglycemia in older or frail adults [29,30]. In clinical practice, glycemic targets should therefore be individualized according to frailty, comorbidity, cognitive status, functional capacity, and treatment burden rather than inferred from the present observational association alone.

These findings support the consideration of routine frailty screening and medication review in older adults with T2DM who are at risk of hypoglycemia. Any adjustment, dose reduction, or discontinuation of insulin or sulfonylurea therapy should be individualized based on glycemic status, treatment goals, renal function, and clinical need. Frailty alone does not establish that insulin should be discontinued. Comprehensive geriatric assessment, nutritional assessment, cognitive evaluation, and individualized glycemic targets may help clinicians balance treatment benefit and hypoglycemia risk [31].

Evidence on newer glucose-lowering agents suggests that SGLT2 inhibitors and GLP-1 receptor agonists may offer cardiovascular and renal benefits with low intrinsic hypoglycemia risk when used appropriately [32-36]. However, the present study did not compare medication strategies, estimate treatment effects, or evaluate medication switching. Accordingly, these agents should be discussed as potential therapeutic options within guideline-based individualized care rather than as direct treatment recommendations arising from this observational study.

This study has several limitations. First, the retrospective design limits causal inference, and residual confounding by unmeasured factors such as dietary intake, physical activity, socioeconomic conditions, medication dose and treatment changes, and access to care remains possible. Second, the FRAIL scale was reconstructed retrospectively from clinical documentation rather than administered prospectively; although inter-rater agreement was excellent, some components may not be equivalent to the original patient-reported instrument. Third, 247 participants with incomplete FRAIL components were excluded. The MICE sensitivity analysis produced a similar estimate, but this does not establish that selection bias was absent. Fourth, eligibility required at least 6 months of observable follow-up. This criterion may preferentially

exclude individuals who experienced early death, transfer, or loss to follow-up; because the current analysis was restricted to participants meeting this criterion, the potential for selection bias cannot be excluded. Fifth, medication exposures were measured at baseline despite a median follow-up of 3.2 years, so treatment changes, dose intensity, and regimen changes could not be fully captured. Sixth, the fully adjusted model included CKD and other variables that may conceptually overlap with components or consequences of frailty. Therefore, the findings should be interpreted as associations adjusted for selected measured baseline covariates rather than a definitive causal model. Seventh, hospital-level clustering was not separately modeled, and within-hospital similarities in documentation, prescribing, admission thresholds, and coding may have led to underestimation of uncertainty. Eighth, hypoglycemia-related events outside the participating hospital network or events managed entirely in the community may have been missed. Finally, the cohort comprised hospital-based participants from five provinces in Sulawesi and was not nationally representative of older adults with T2DM in Indonesia. Mortality was an important competing event in this cohort, with 198 deaths (6.9%) during follow-up. The Fine–Gray analysis produced estimates consistent in direction with the primary Cox model, supporting the robustness of the association under a competing-risk framework. Nevertheless, the two approaches estimate different quantities, and agreement between them should not be interpreted as proof that informative censoring was absent.

Conclusion

Frailty was associated with a higher hazard of hypoglycemia-related emergency department visits or hospitalizations among adults aged ≥60 years with T2DM. The association was directionally consistent in sensitivity and competing-risk analyses. These findings provide evidence from 10 hospitals across five provinces in Sulawesi, Indonesia, but should not be interpreted as nationally representative. Routine frailty screening and individualized review of glycemic treatment may help identify patients at increased risk, although prospective and interventional studies are needed to determine whether frailty-guided management reduces hypoglycemia-related acute care use.

Ethics approval

Ethics approval was granted by the Health Research Ethics Committee of Muhammadiyah University of Gorontalo (No. 089/KEPK-FIKES/VIII/2025). Given the retrospective nature of this study, which relied exclusively on pre-existing electronic medical records and hospital administrative databases, the ethics committee waived the requirement for individual written informed consent. This waiver was granted on the basis that the study involved no direct patient contact, posed minimal risk to participants, and that obtaining consent from all 2,847 participants—whose records spanned from January 2021 to December 2025—would be impracticable. All data were de-identified prior to analysis to ensure participant confidentiality and anonymity. This study was conducted in accordance with the Declaration of Helsinki and applicable national regulations governing the use of medical records for research purposes.

Acknowledgments

The authors thank the participating hospitals and medical-record teams for supporting data access and verification. We also acknowledge the institutional support provided by the Muhammadiyah University of Gorontalo.

Competing interests

The authors declare no competing interests.

Funding

This research was funded by the Ministry of Higher Education, Science and Technology of Indonesia with grant number 1211.2/2025.kemenristekdikti.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request. Supplementary data are available at https://doi.org/10.5281/zenodo.23718666.

Declaration of artificial intelligence use

Artificial intelligence tools (ChatGPT, OpenAI, San Francisco, CA, USA) were used to assist in language editing, refinement of sentence structure, and improvement of readability. The authors reviewed and verified all content to ensure accuracy and scientific integrity. AI was not used for data analysis, result generation, or interpretation.

How to cite

Ilham R, Febriyona R, Ishak F. Frailty status and risk of hypoglycemia-requiring hospital care among older adults with type 2 diabetes in Sulawesi, Indonesia: A retrospective cohort study. Narra X 2026; 4 (3): e340 - http://doi.org/10.52225/narrax.v4i3.340.

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