

Subphenotypes of Joint Dynamic Trajectories of Caloric Adequacy Rate and Protein Intake in the Acute Phase of ICU: Dynamic Stratification Evidence and a Clinical Tool

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Abstract

Background & Aims:

This study used group-based multi-trajectory modeling (GBTM) to identify subphenotypes of the joint dynamic trajectories of caloric adequacy rate and protein intake within the first 7 days after ICU admission and to examine their association with 30-day mortality.

Methods:

This retrospective study utilized single- and dual-trajectory group-based trajectory modeling (GBTM) to identify latent subgroups in the MIMIC-IV cohort, with validation of the dual-trajectory model in the GMU-ICU cohort. Patients aged ≥ 18 years with a first ICU stay > 7 days were included, while those with repeat ICU admissions, missing energy intake data within 7 days, or missing body weight data were excluded. GBTM was applied to model trajectories of caloric intake (kcal/kg/day) and protein intake (g/kg/day). Optimal group numbers were selected based on Bayesian information criterion (BIC), average posterior probability, and other metrics. Kaplan-Meier curves compared 30-day survival differences, and multivariable logistic regression adjusted for confounders (age, APACHE II score, comorbidities, etc.) was employed to evaluate trajectory group associations with mortality risk.

Results:

A total of 4,170 patients were included in the MIMIC cohort. The single-trajectory model for caloric adequacy identified an optimal 5 groups, with survival analysis showing no significant differences in 30-day mortality across groups. In the dual-trajectory model combining caloric intake and protein intake, 5 groups were similarly retained in the MIMIC-IV cohort, demonstrating significant heterogeneity in baseline characteristics. Group δ , characterized by early acute-phase caloric intake reaching approximately 70%, progressively escalating to 100%, and protein intake gradually increasing to 1.2–1.3 g/kg/d, exhibited the lowest mortality. After adjusting for confounders, mortality risk remained significantly higher in other groups compared to Group δ . Trends in the GMU-ICU cohort were consistent with those in the MIMIC cohort, although the overfeeding group (Group 5) had the highest mortality.

Conclusion:

Single-trajectory analysis of caloric adequacy showed no significant association with 30-day mortality, whereas the joint caloric-protein trajectory significantly stratified prognostic risk. This is the first study to identify the optimal nutritional trajectory subphenotype (Group δ) using dual-trajectory GBTM and validate its independent protective effect in two independent cohorts. The model provides real-world dynamic stratification evidence for current guidelines and proposes a potential clinical tool for individualized precision nutrition.

Background

In recent years, nutritional support strategies for energy and protein during the acute phase (first 1–7 days of ICU admission) of critical illness have undergone significant evolution [1, 2]. Regarding caloric targets in the acute phase, multiple guidelines recommend initiating restrictive feeding ($< 70\%$ of measured or estimated energy expenditure) with progressive escalation to 70%–100% to mitigate overfeeding-related complications. However, studies have demonstrated no substantial differences in short-term mortality between low- and high-dose energy provision [2, 3]. Concurrently, protein intake targets remain contentious, with several large randomized controlled trials indicating that excessive protein provision (> 2.0 g/kg/d) in the acute phase fails to improve clinical outcomes

and may even heighten mortality risk in subgroups with acute kidney injury, prompting a shift in clinical practice from early full feeding to a paradigm of restrictive energy with progressive protein augmentation [4–7].

Traditional nutrition support emphasized non-protein calorie-to-nitrogen ratios (NPC:N 100–150:1) to achieve a protein-sparing effect, but accumulating evidence has refuted this bundled approach, advocating instead for independent targeting of energy and protein [7]. In contemporary clinical practice, enteral or parenteral prescriptions frequently combine energy and protein, making it challenging to adjust them separately, increasing workload complexity, and leaving the dynamic interactions between energy and protein—and their combined prognostic impact—poorly elucidated [8]. Although current guidelines endorse "energy restriction with independent protein optimization," direct comparative research on high-protein hypocaloric versus moderate-protein hypocaloric feeding is scarce, contributing to ongoing uncertainty in nutritional prescribing [4, 7, 9].

Previous studies evaluated cumulative caloric or protein deficits and adequacy rates separately. However, none have used group-based multi-trajectory modeling (GBTM) to simultaneously characterize the joint dynamic trajectories of caloric adequacy rate and protein intake during ICU admission, thereby overlooking their dynamic synergistic interaction. This study is the first to apply GBTM to identify caloric-protein dual-trajectory subphenotypes, providing real-world dynamic stratification evidence for current guidelines and a clinically applicable precision nutrition tool.[10]

Methods

Data Sources and Study Population

The MIMIC-IV database comprises de-identified patient information collected from intensive care units and emergency departments at Beth Israel Deaconess Medical Center, spanning data from 2008 to 2019 [11]. The database is freely downloadable following completion of an official certification course. Author has completed this certification and is permitted to extract data. The GMU-ICU database includes all ICU patient data from the Affiliated Hospital of Guizhou Medical University collected between 2021 and 2024. The present study is reported in accordance with guidelines developed for observational research using routinely collected health data [12].

Inclusion/Exclusion Criteria and Data Collection

This study focused on patients with first-time admission to general ICU managing a broad spectrum of critically ill patients. Inclusion criteria were: 1. age ≥ 18 years; 2. first ICU length of stay > 7 days (to align with guideline recommendations for gradual target achievement over 7 days and to minimize missing data). Exclusion criteria were: 1. repeat ICU admissions; 2. no energy provision within the first 7 days (as absence of any energy or protein provision in the acute phase indicates extremely poor prognosis likely driven by acute factors); 3. missing body weight data. The target daily caloric intake was set at 25 kcal per kilogram of actual body weight, with energy adequacy calculated as prescribed energy divided by target caloric intake. The primary outcome was 30-day mortality following ICU admission. Twenty-seven variables were selected, encompassing demographic characteristics, vital signs, laboratory parameters, comorbidities, and ICU-related severity scores, all collected within the first 24 hours of ICU admission. To ensure data integrity, the MIMIC cohort was derived from MIMIC-IV patients meeting inclusion/exclusion criteria between 2008 and 2019. For temporal consistency and external validation, the GMU-ICU cohort comprised patients from the Affiliated Hospital of Guizhou Medical University

(2022–2024) meeting the same criteria. In order to minimize selection bias, we removed variables with over 30% missing values and imputed the remaining variables ($\leq 30\%$ missing) using the K-nearest neighbor (KNN) algorithm.

Ethics and Informed Consent Statement

The research protocol was examined and approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University (approval date: December 27, 2023; approval number: 2023 – 918). The study was an exploratory retrospective analysis of ICU nutritional adequacy. As all data were sourced from de-identified electronic health records with no traceability to individual identities, informed consent was waived. The study strictly complied with the Declaration of Helsinki and relevant national ethical regulations for human research, fully protecting participant privacy through anonymized data extraction, storage, and analysis, with no disclosure of personal information.

Single- and Dual-Trajectory Model Construction

Single-trajectory modeling of energy adequacy was performed first to evaluate the independent prognostic impact of dynamic energy provision. Group-based trajectory modeling (GBTM) was applied to estimate daily energy adequacy trajectories over the first 7 ICU days [10, 13]. The model assumes the population comprises a finite number of latent trajectory groups, with group membership probabilities estimated via multinomial logit functions using maximum likelihood. Energy adequacy was modeled with a censored normal (cnorm) distribution. For each trajectory group, intercept, linear, quadratic, and cubic polynomial terms were sequentially tested, retaining the highest-order significant term ($P < 0.05$). Model selection was iterative, starting from 2 groups and increasing to a maximum of 8. Optimal group number and polynomial order were determined comprehensively using: (1) Bayesian information criterion (BIC), selecting the model closest to 0 with $|\Delta\text{BIC}| > 10$ indicating strong evidence for additional groups; (2) average posterior probability (AvePP) ≥ 0.70 per group; (3) overall entropy > 0.80 , indicating high classification quality. Final single-trajectory models were selected when further increases in groups or polynomial order yielded no significant improvements. Patients were assigned to trajectory groups based on maximum a posteriori probability.

Dual-trajectory modeling of energy adequacy and protein intake was then conducted to explore their dynamic interactions and joint prognostic effects. Group-based multi-trajectory modeling was employed, allowing simultaneous trajectory estimation for multiple time-varying outcomes. Both energy (kcal/kg/day) and protein intake (g/kg/day) were modeled with censored normal distributions. Polynomial testing (intercept to cubic) was performed separately for each outcome within groups, retaining significant terms ($P < 0.05$). Model selection criteria mirrored those for single-trajectory modeling. Subsequently, multivariable logistic regression was used to assess associations of single- and dual-trajectory groups with 30-day mortality, referencing the optimal energy adequacy or lowest-mortality group.

Statistical Analysis

Categorical data were summarized as counts (percentages), with comparisons between groups performed using χ^2 tests or Fisher's exact tests. Continuous data were expressed as medians (interquartile ranges) and analyzed with the Mann-Whitney U tests. Group-based trajectory modeling (single and multi) was implemented in R using the gbmt package. Multivariable logistic regression for confounder adjustment was performed using R's stats package. Data preprocessing was conducted in Python 3.6.5, with GBTM and regression analyses in R 4.0.2.

Results

Flowchart and Baseline Characteristics of the MIMIC-IV Cohort

From 2008 to 2019, 8065 patient records were initially screened in the MIMIC-IV database. After excluding repeat ICU admissions ($n = 1116$), patients with no energy provision within the first 7 days ($n = 3$), and those with missing body weight data ($n = 2776$), 4170 patients were included in the MIMIC-IV cohort. In the GMU-ICU cohort (2022–2024), 1208 records were screened, excluding repeat ICU admissions ($n = 104$), no energy provision within 7 days ($n = 2$), and missing body weight ($n = 37$), resulting in 1065 patients (Fig. 1). Baseline characteristics of the MIMIC-IV cohort and GMU-ICU cohort are shown in Supplementary Table 1 and Supplementary Table 2.

Single-Trajectory Modeling of Caloric Adequacy and Kaplan-Meier Analysis in the MIMIC-IV Cohort

Single-trajectory modeling was conducted using daily caloric adequacy over the first 7 ICU days, with the optimal model retaining 5 groups based on BIC (Supplementary Table 3). Group D was characterized by caloric adequacy increasing from $\sim 30\%$ in the early acute phase (days 1–3) to 70%, then nearly reaching 100% in the late acute phase (days 4–7). Group B (the largest) exhibited a very slow rise from 21% to 44% over 7 days. Group E maintained very low levels in the first 2 days, followed by a rapid increase from day 3, exceeding 50% by day 7. Group A started at $\sim 18\%$ on day 1, gradually decreased over the subsequent 3 days, and fluctuated around 10% in the late phase. Group C showed persistently low adequacy, with virtually no caloric provision throughout the 7 days. Group D most closely aligned with guideline-recommended caloric prescribing ($\leq 70\%$ early acute phase progressing to near 100% late phase), while the other groups (A, B, C, E) did not. Kaplan-Meier analysis yielded 30-day mortality rates of 14.8%, 11.1%, 13.7%, 10.9%, and 13.6% across the five groups, respectively; Group D had the lowest rate, but intergroup differences were not significant ($P = 0.054$) (Fig. 2).

Dual-Trajectory Modeling of Caloric Adequacy and Protein Intake and Kaplan-Meier Analysis in the MIMIC-IV Cohort

Dual-trajectory modeling of caloric adequacy and protein intake over the first 7 days identified an optimal 5 groups based on BIC (Supplementary Table 2). Group δ demonstrated caloric adequacy starting at $\sim 40\%$ and progressively exceeding 70%, with protein intake rising from 0.6 g/kg/day in the early acute phase (days 1–3) to 1.2 g/kg/day, stabilized thereafter. Group β showed a rapid increase in caloric adequacy from 20% to 70% over the first 4 days, alongside protein intake rapidly rising from ~ 0.1 g/kg/day to 0.9 g/kg/day, with no further escalation. Group α exhibited slow progression: caloric adequacy $\sim 20\%$ and protein ~ 0.1 g/kg/day in the first 3 days, gradually reaching $\sim 50\%$ caloric adequacy and ~ 0.6 g/kg/day protein by day 7. Group γ began at $\sim 21\%$ caloric adequacy and ~ 0.18 g/kg/day protein, with minor initial rises followed by declines (maximum $\sim 25\%$ caloric adequacy and ~ 0.4 g/kg/day protein). Group ϵ received virtually no energy or protein over the 7 days (Fig. 3). Thirty-day mortality rates for Groups α – ϵ were 13.7%, 13.7%, 11.3%, 6.4%, and 13.0%, respectively, with Group δ showing the lowest ($P < 0.001$) (Fig. 4A).

Baseline Characteristics and Logistic Regression for Dual-Trajectory Groups in the MIMIC-IV Cohort

In the MIMIC-IV cohort, significant differences between groups were evident for most variables ($P < 0.05$), except for a few (gender, chronic kidney disease, D-dimer) (Table 1). Group δ lacked obvious baseline advantages in age, APACHE II score, underlying diseases, comorbidities, or 24-hour post-admission laboratory results. Unadjusted logistic regression (Model 1) showed a higher 30-day mortality risk in all other groups compared to Group δ ($P < 0.05$). After adjusting for confounders (Model 2: age, APACHE II, analgesic drugs, sedative drugs, APTT, albumin, D-dimer, INR, platelets, phosphate, AKI, chronic renal failure, liver disease, respiratory disease, arterial hypertension, sepsis, diabetes), elevated risk persisted in Group α (OR 1.66, 95% CI 1.08–2.54, $P = 0.021$) and Group ε (OR 1.73, 95% CI 1.11–2.72, $P = 0.016$) relative to Group δ (Fig. 5).

Table 1
Main characteristics of the patients in MIMIC Dual Trajectory

Characteristic	Total (n = 4170)	Group α (n = 1462)	Group β (n = 1196)	Group γ (n = 203)	Group δ (n = 450)	Group ϵ (n = 859)	P value
Age, year	63 (53, 73)	62 (52, 72)	64 (53, 74.25)	62 (55, 73)	64 (53, 74)	63 (52, 73)	0.045
Male, sex	2427 (58.20%)	863 (59.03%)	693 (57.94%)	108 (53.20%)	272 (60.44%)	491 (57.16%)	0.427
Body mass index, kg/m ²	27.8 (23.9, 33)	28.55 (24.5, 33.67)	27.9 (24.32, 32.8)	28.44(24.4, 34.05)	26.4 (22.5, 31.5)	27.021(23.2, 31.9)	< 0.001
APACHE	29 (24, 35)	29 (24, 35)	30 (25, 34)	30 (24, 35)	30 (25.25, 36)	28 (23, 34)	< 0.001
Sepsis	1012 (24.27%)	358 (24.49%)	199 (16.64%)	63 (31.03%)	158 (35.11%)	234 (27.24%)	< 0.001
Comorbidities							
AKI	1537 (36.86%)	554 (37.89%)	400 (33.44%)	86 (42.36%)	198 (44.00%)	299 (34.81%)	0.004
Arterial hypertension	1414 (33.91%)	489 (33.45%)	377 (31.52%)	64 (31.53%)	174 (38.67%)	310 (36.09%)	0.039
Diabetes	971 (23.29%)	336 (22.98%)	259 (21.66%)	50 (24.63%)	136 (30.22%)	190 (22.12%)	0.005
Chronic renal failure	137 (3.29%)	41 (2.80%)	37 (3.09%)	13 (6.40%)	19 (4.22%)	27 (3.14%)	0.068
Liver Disease	519 (12.45%)	189 (12.93%)	126 (10.54%)	34 (16.75%)	61 (13.56%)	109 (12.69%)	0.080
Respiratory Disease	3401 (81.56%)	1287 (88.03%)	744 (62.21%)	181 (89.16%)	417 (92.67%)	772 (89.87%)	< 0.001
Drug Analgesic	2822 (67.67%)	1027 (70.25%)	669 (55.94%)	158 (77.83%)	348 (77.33%)	620 (72.18%)	< 0.001
Drug Sedation	2400 (57.55%)	921 (63.00%)	427 (35.70%)	127 (62.56%)	328 (72.89%)	597 (69.50%)	< 0.001
Laboratory tests on the first day							
Lactate	2.3 (1.567, 3.6)	2.6 (1.6, 4.053)	2.237 (1.6, 3.4)	2.1 (1.6, 3.463)	2.3 (1.6, 3.6)	2.2 (1.471, 3.298)	< 0.001
BNP	4887.6 (2516.87, 10526.58)	4924.05 (2516.87, 11191.7)	4967.77 (2757.42, 10369.267)	4887.6 (2497.22, 11163.945)	4626.86 (2497.22, 10454.988)	4887.6 (2516.87, 10476.04)	0.829

Data are presented as median (IQR) or n (%). P values were calculated using χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; ALb, albumin; D-D, D-dimer; INR, international normalized ratio; PLT, platelets; WBC, white blood cell count; pCO₂, partial pressure of carbon dioxide; CK, creatine kinase; RBC, red blood cell count; BNP, brain natriuretic peptide.

Characteristic	Total (n = 4170)	Group α (n = 1462)	Group β (n = 1196)	Group γ (n = 203)	Group δ (n = 450)	Group ϵ (n = 859)	P value
APTT	29.3 (26.4, 33.935)	29.701 (26.6, 34.575)	29.35 (26.6, 34.7)	29.2 (26.4, 32.9)	28.745 (25.9, 32.259)	28.9 (26.1, 33.4)	0.001
ALb	3.072 (2.7, 3.4)	3 (2.661, 3.4)	3.1 (2.747, 3.415)	3.027 (2.705, 3.327)	3.1 (2.621, 3.431)	3.1 (2.675, 3.423)	0.042
D-D	2955.85 (1957.06, 5665.73)	2955.85 (1911.697, 5337.42)	2955.85 (1975.06, 6181.94)	2955.85 (1783.96, 5219.4)	3116.515 (1975.06, 6223.59)	2955.85 (1975.06, 5278.41)	0.474
INR	1.2 (1.1, 1.4)	1.2 (1.1, 1.4)	1.2 (1.1, 1.4)	1.2 (1.1, 1.4)	1.2 (1.1, 1.3)	1.2 (1.1, 1.4)	< 0.001
PLT	146 (93, 206)	139 (85, 201)	151 (105, 220.25)	150 (75.5, 202)	138 (92, 191)	155 (101, 209.5)	< 0.001
WBC	0 (0, 2)	1 (0, 2)	0 (0, 1)	1 (0, 2)	1 (0, 2)	0 (0, 2)	< 0.001
pCO ₂	35 (31, 40)	34 (30, 39)	35.17 (31, 40)	36 (32, 42)	34.855 (30, 40)	35 (31, 41)	0.004
CK	232.22 (94, 738.165)	254.93 (98.297, 811.115)	238.72 (106.797, 734.227)	191.65 (83, 602.175)	176 (64.25, 539.59)	231.56 (92.03, 763.26)	0.002
Phosphate	3 (2.3, 3.668)	3 (2.32, 3.8)	3.1 (2.5, 3.8)	2.7 (2.2, 3.4)	2.6 (2.1, 3.1)	2.8 (2.3, 3.5)	< 0.001
RBC	2.99 (2.54, 3.57)	3.02 (2.58, 3.587)	3.16 (2.69, 3.7)	2.81 (2.39, 3.31)	2.6 (2.31, 3.02)	2.98 (2.47, 3.61)	< 0.001
Hemoglobin	8.8 (7.6, 10.5)	9 (7.7, 10.6)	9.3 (8, 10.9)	8.2 (7.2, 9.75)	7.7 (6.9, 8.9)	8.7 (7.4, 10.6)	< 0.001
Death at day 30	529 (12.69%)	201 (13.75%)	164 (13.71%)	23 (11.33%)	29 (6.44%)	112 (13.04%)	0.008

Data are presented as median (IQR) or n (%). P values were calculated using χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; ALb, albumin; D-D, D-dimer; INR, international normalized ratio; PLT, platelets; WBC, white blood cell count; pCO₂, partial pressure of carbon dioxide; CK, creatine kinase; RBC, red blood cell count; BNP, brain natriuretic peptide.

Dual-Trajectory Modeling and Kaplan-Meier Analysis in the GMU-ICU Validation Cohort

In the GMU-ICU cohort, Group 1 most closely approached guideline recommendations: restrictive early-phase caloric provision with gradual late-phase increase (though remaining < 70% by day 7), alongside protein intake progressively reaching 1.2 g/kg/day over 7 days. Group 3 maintained caloric adequacy < 50% throughout but exceeded 1.3 g/kg/day protein in the late phase. Group 5 received full early caloric provision (100% adequacy) and protein (1.3 g/kg/day), with mild subsequent declines (Fig. 6). Thirty-day mortality rates for Groups 1–5 were 25.7%,

37.5%, 26.4%, 37.3%, and 47.5%, respectively. No group fully adhered to current guidelines, yet Groups 1 and 3 had comparatively lower mortality, while Group 5 (overfeeding) had the highest (Fig. 4B).

Discussion

This is the first study to use group-based multi-trajectory modeling (GBTM) to simultaneously construct the joint dynamic trajectories of caloric adequacy rate and protein intake, providing real-world dynamic stratification evidence for the “restrictive caloric feeding plus stepwise adequate protein” strategy recommended by the ESPEN 2023 and ASPEN 2022 guidelines. Compared with previous studies, this dual-trajectory GBTM approach fully characterized the joint dynamic trajectories of caloric adequacy and protein intake during the first 7 days in the ICU. It is the first to demonstrate an independent association between the optimal joint trajectory and 30-day mortality in the MIMIC-IV cohort. Single-trajectory analysis of caloric adequacy failed to stratify 30-day prognostic risk ($P > 0.05$), whereas the dual-trajectory model accurately stratified 30-day mortality from 13.7% (highest) to 6.4% (lowest) .

Our results showed no significant association between single-energy trajectory subgroups and 30-day mortality (log-rank $P = 0.054$), consistent with several recent large-scale studies suggesting limited independent prognostic impact of varying acute-phase energy strategies [14–16]. Potential explanations include: first, marked early metabolic heterogeneity in critically ill patients, where energy requirements fluctuate with stress hormones, inflammation, and organ dysfunction, resulting in mismatch between static caloric adequacy and dynamic metabolic demands and reduced statistical power [17]; second, although guidelines have shifted toward hypocaloric feeding ($< 70\%$ target) to avert hyperglycemia, refeeding syndrome, and infection risks associated with early full feeding, this may obscure potential benefits of moderate energy provision [7]; third, short-term outcomes (e.g., 30-day mortality) are predominantly driven by baseline severity (e.g., SOFA score) and acute complications, with energy effects potentially manifesting later in recovery (> 7 days) [18]. Additionally, observational biases, residual confounding, and inaccuracies in nutrition recording (e.g., omitting parenteral contributions) further attenuate associations with isolated energy metrics [1].

The optimal dual-trajectory group (Group δ : energy progressively exceeding 70% in the acute phase + protein reaching 1.2–1.3 g/kg/day) exhibited the lowest 30-day mortality (6.4%), providing clinical evidence for the “hypocaloric with adequate protein” paradigm endorsed by guidelines. This pattern aligns closely with ESPEN 2023 and ASPEN 2022 recommendations, avoiding early overfeeding risks (e.g., suppressed autophagy, exacerbated insulin resistance) while progressively escalating energy to maintain metabolic homeostasis [4, 7]. Excessive energy burden may induce hepatic steatosis, refeeding syndrome, and persistent hyperglycemia from high carbohydrate loads [19]. Early RCT evidence suggests “hypocaloric with adequate protein” strategies may reduce organ failure and hyperglycemia, though benefits for mechanical ventilation duration, ICU stay, and functional recovery require confirmation in larger trials [20]. Finally, in patients with high nutritional risk, lower early energy intake confers greater infection reduction benefits [21].

The joint caloric-protein trajectory analysis showed a significant prognostic association ($P < 0.001$), highlighting the interaction between caloric intake and protein supply. This interaction is likely mediated by the classic AMPK-mTORC1-autophagy signaling axis: excess glucose suppresses AMPK and activates mTORC1 by lowering the AMP/ATP ratio, thereby inhibiting autophagy, leading to accumulation of damaged organelles, increased oxidative stress, and organ injury [22–24]. In contrast, moderate caloric restriction activates AMPK, which phosphorylates and inhibits mTORC1 while initiating ULK1-mediated autophagy; when combined with progressively adequate

amino acids, this results in only moderate mTORC1 activation, preserving autophagic protection while supporting muscle protein synthesis and nitrogen balance, thereby achieving dynamic equilibrium in the AMPK-mTORC1 axis[25, 26]. On this basis, the FOXO-mediated urea cycle-gluconeogenesis coupling axis (FOXO-Ass1) further strengthens the synergy: insufficient glucose activates FOXO, promoting amino acid nitrogen reutilization and gluconeogenesis; appropriate amino acids provide substrates to achieve dynamic nitrogen-energy balance [27, 28]. Glutamine-glucose TCA cycle anaplerosis and nitrogen cycling via GLS-generated α -KG support immune cell energy demands and muscle homeostasis[29, 30]. The Sirtuin family (SIRT1/4/5) acts as a nutrient sensor, integrating multiple glucose-amino acid pathways to restore metabolic balance under critical illness-induced oxidative stress [31].

These synergistic interactions explain why single caloric trajectories fail to stratify 30-day mortality risk, whereas the joint caloric-protein trajectory precisely identifies the optimal subphenotype (Group δ), providing a solid mechanistic basis for the “low caloric intake with adequate protein” strategy. Clinically, precise nutrition (indirect calorimetry plus protein monitoring) is required to improve post-intensive care syndrome (PICS)[32]. Future integration of trajectory modeling with omics data may further elucidate epigenetic interactions and strengthen the theoretical foundation for clinical strategies [33].

Limitations

This observational study used multivariable logistic regression to control for confounders, yet residual confounding cannot be fully excluded. By focusing on dynamic trajectories of medium- to long-term nutritional support and selecting a 7-day (rather than 3-day) window, the study more comprehensively captured the gradual achievement of caloric adequacy rate and protein intake. However, the inclusion criterion requiring ICU stay > 7 days may introduce survivor bias by systematically excluding the most critically ill patients who died or were transferred within the first 7 days. These patients typically had the highest severity and lowest nutritional adequacy rates, and their early deaths may be directly linked to inadequate nutritional support. Consequently, the cohort is biased toward medium- to long-term survivors, potentially underestimating the association between unfavorable nutritional trajectories and short-term mortality while limiting generalizability to the broader critically ill population. In addition, the mechanistic understanding of energy-protein interactions remains limited and may have overestimated their synergistic effects, requiring validation by metabolomics. No subgroup analysis by nutrition delivery route was performed, and the fixed energy target (25 kcal/kg/day) lacked individualization (e.g., indirect calorimetry). Future studies should refine subgroup analyses (e.g., by feeding route) or include additional variables (such as blood glucose and prealbumin) for sensitivity analyses.

Conclusion

Joint trajectories of caloric and protein supply in the early ICU phase significantly influence prognosis. This is the first study to provide real-world dynamic stratification evidence for current guidelines using a dual-trajectory GBTM model and to propose a precision nutrition tool directly applicable to clinical practice. The model highlights the necessity of dynamic joint assessment of both indicators and holds promise in advancing critical care nutrition from empirical treatment to individualized precision nutrition.

Declarations

Conflicts of Interest:

The authors declare no conflicts of interest.

Ethical Approval and Consent to participate:

The research protocol was approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University (approval number: 2023 – 918; approval date: December 27, 2023). This study was a retrospective analysis based on de-identified electronic health records. The requirement for informed consent was waived by the Ethics Committee because all data were anonymized and could not be traced to individual patients.

Consent for publication:

Not applicable.

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Author Contribution

J.X.: conceptualization, study design, and manuscript writing; L.W.: Resources and Validation; S.T.: data extraction; H.B.: manuscript writing; Y.T.: conceptualization, study supervision, and manuscript revision.

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Data Availability

De-identified derived datasets and analysis code generated during the current study are available in the GitHub repository, <https://github.com/xiongmaodaxia13/icu-nutrition-trajectory>.

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Figures

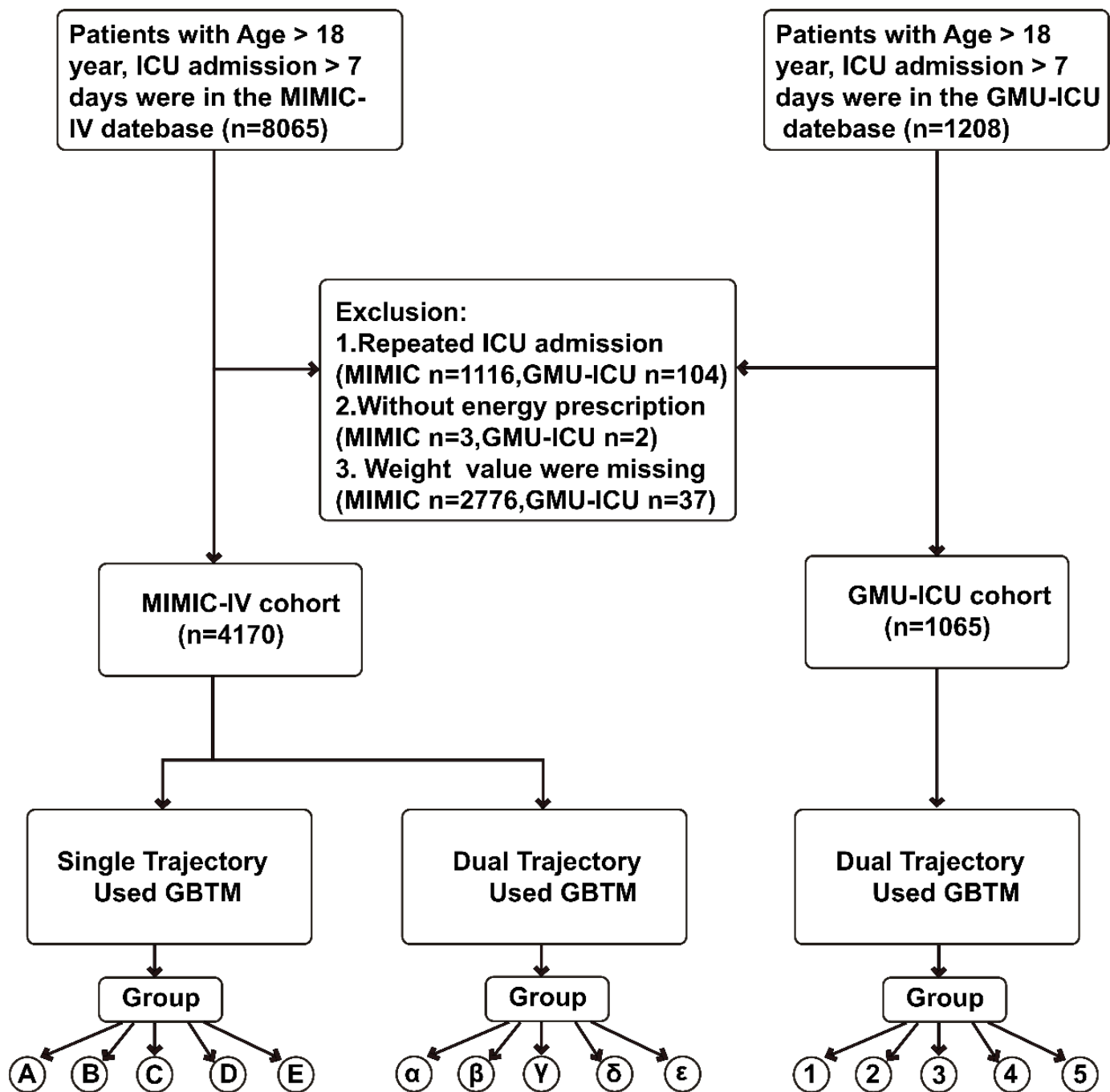


Figure 1

Study flowchart showing patient selection in the MIMIC-IV cohort and GMU-ICU cohort.

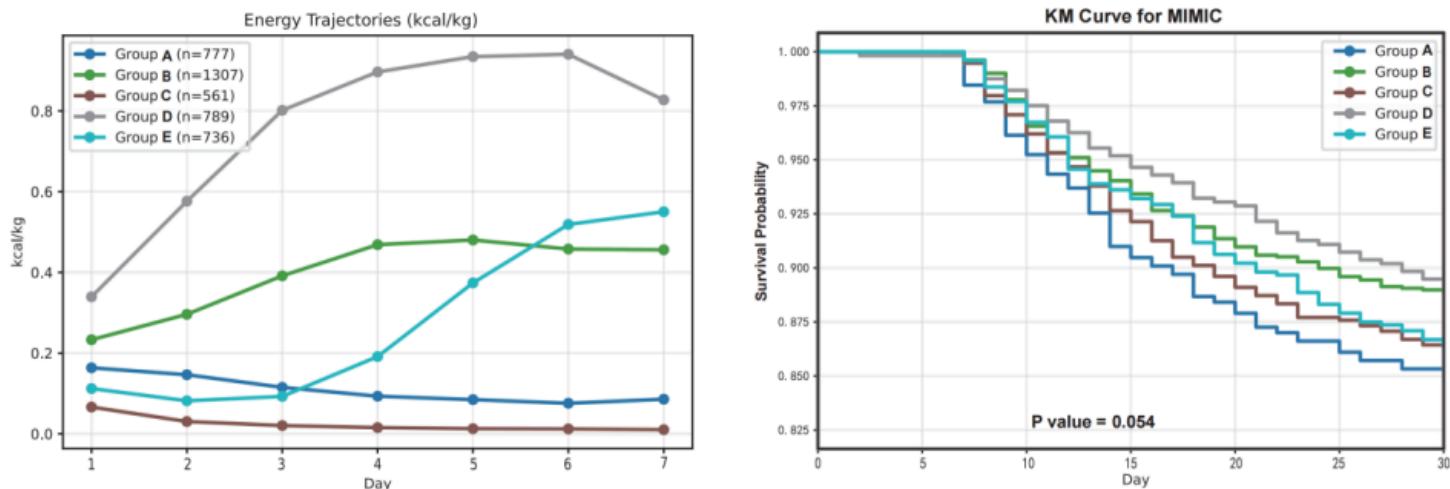


Figure 2

Single-trajectory modeling of energy adequacy over the first 7 ICU days in the MIMIC cohort. Trajectories of daily energy adequacy (%) for the five identified groups (Groups A–E). Kaplan-Meier curves for 30-day mortality across the five single-trajectory groups (P=0.054).

MIMIC Dual Trajectory

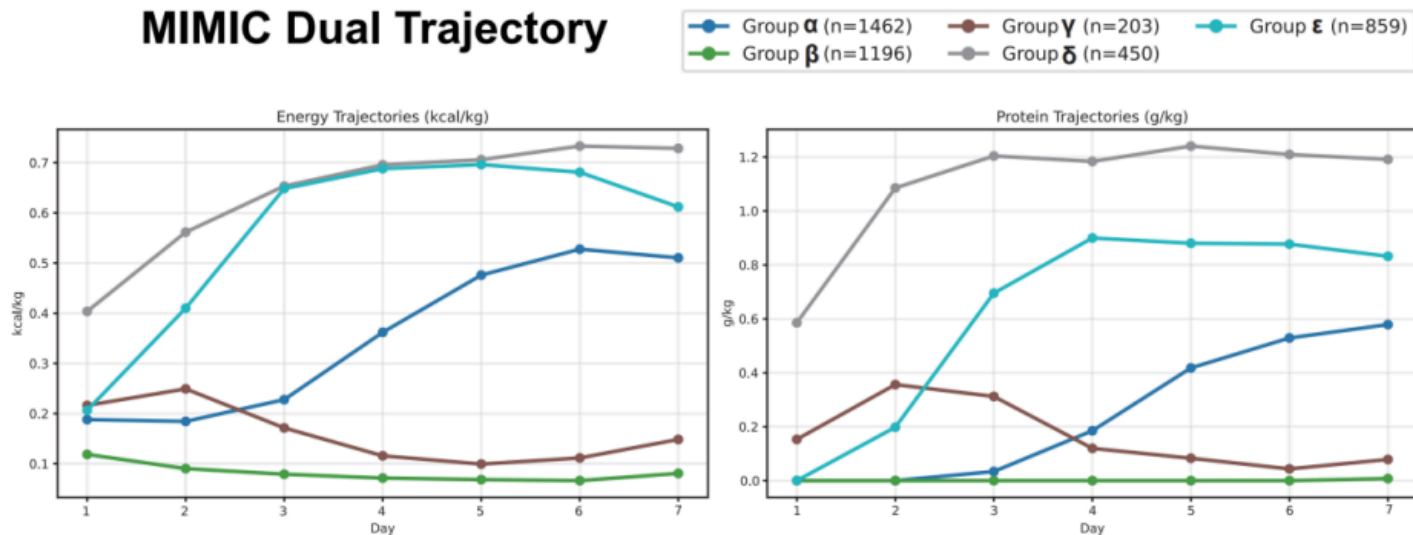


Figure 3

Dual-trajectory modeling of energy adequacy and protein intake over the first 7 ICU days in the MIMIC cohort. Trajectories of daily energy adequacy (%) and protein intake (g/kg/day) for the five identified groups (Groups α – ϵ). Group δ represents the optimal pattern with progressive energy escalation and protein attainment of 1.2–1.3 g/kg/day.

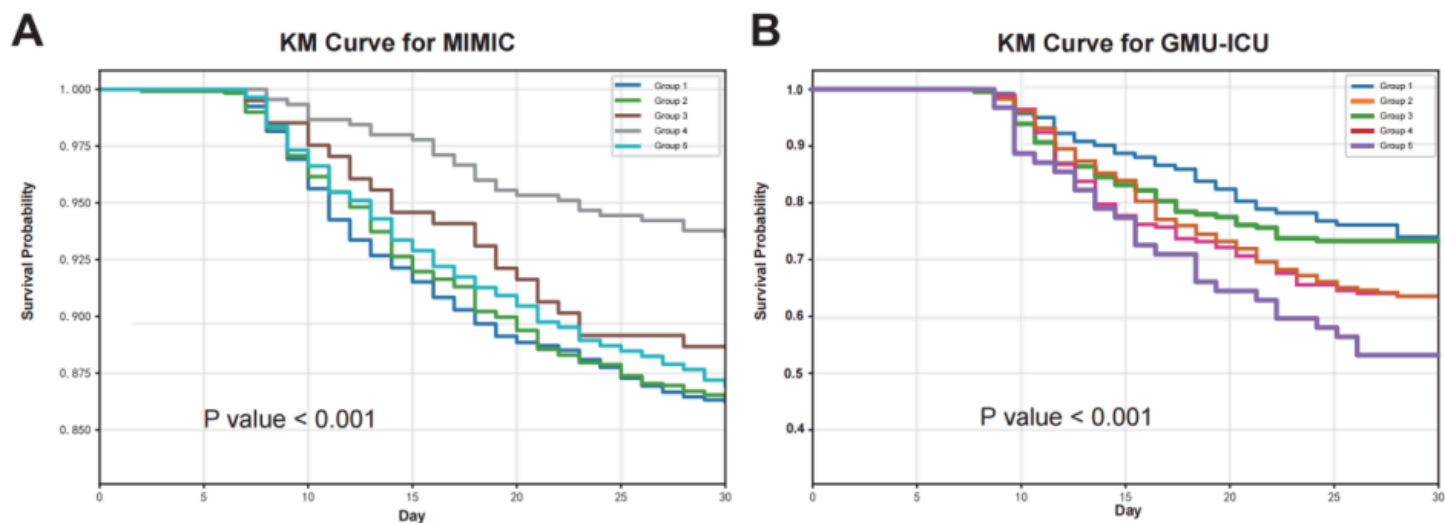


Figure 4

Kaplan-Meier curves for 30-day all-cause mortality according to dual-trajectory groups. (A) MIMIC cohort. (B) GMU-ICU cohort.

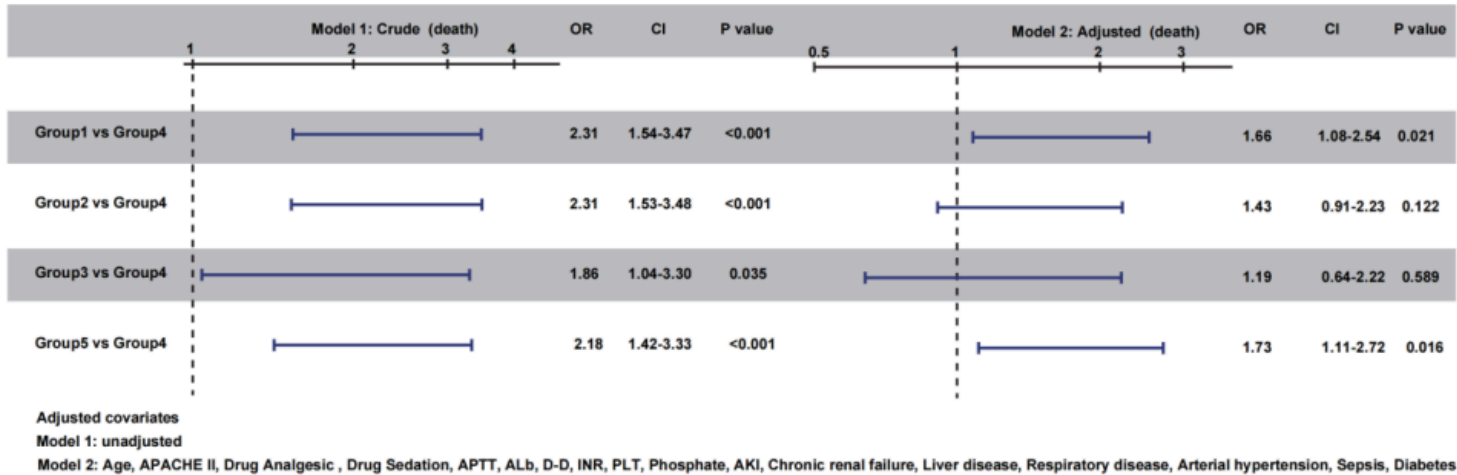


Figure 5

Association of dual-trajectory groups with 30-day mortality in the MIMIC cohort.

GMU-ICU Dual Trajectory

Group 1 (n= 144) Group 3 (n=216) Group 5 (n= 61)
 Group 2 (n= 453) Group 4 (n=193)

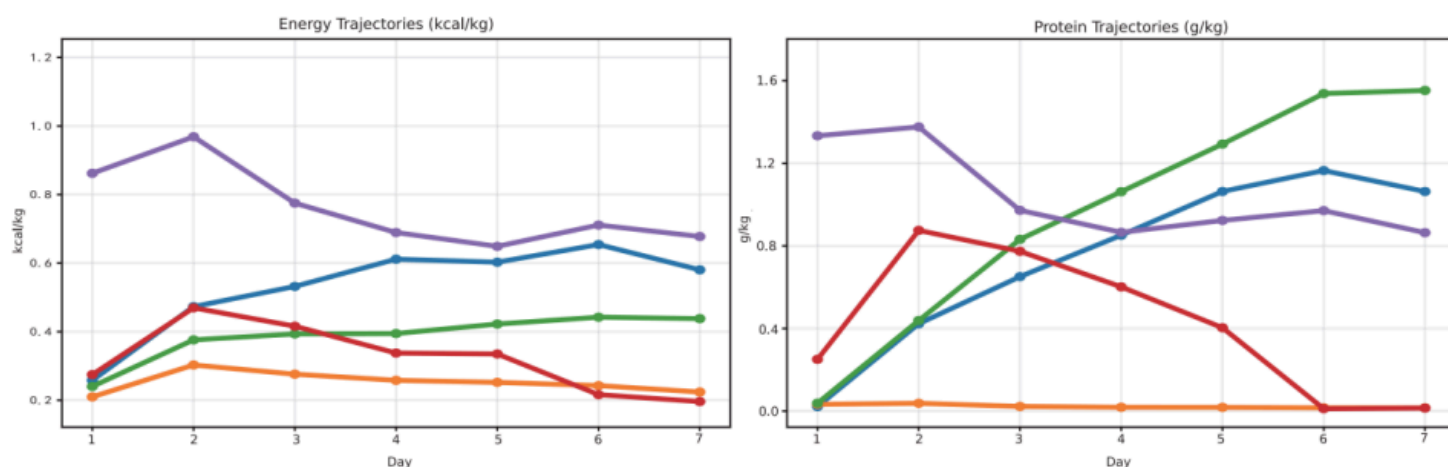


Figure 6

Dual-trajectory modeling of energy adequacy and protein intake over the first 7 ICU days in the GMU-ICU cohort. Trajectories of daily energy adequacy (%) and protein intake (g/kg/day) for the five identified groups (Groups 1–5).

Supplementary Files

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