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Article

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Early Glucose Decline Rate After Insulin Therapy and Subsequent Adverse Metabolic Events in Critically Ill Patients

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Abstract

Insulin is commonly used to treat high blood glucose in critically ill patients, but glucose levels decline at different rates after treatment. Whether this early response is associated with subsequent metabolic complications remains unclear. We analysed data from 10,933 adults receiving insulin for hyperglycaemia in the MIMIC-IV database. The glucose decline rate was measured during the first six hours after insulin initiation, and subsequent complications were assessed over the following 24 hours or until intensive care discharge. Low blood glucose occurred in 811 patients, including 244 with severely low levels. The relationship between glucose decline rate and subsequent low blood glucose was non-linear, varied over time, and differed between intravenous and subcutaneous insulin administration. Faster glucose decline was associated with greater risk during the earliest follow-up period. Glucose decline rate was also associated with low blood potassium, but not consistently with acute kidney injury. These findings suggest that the early glucose response to insulin may help identify patients needing closer glucose and potassium monitoring. Its potential value in short-term metabolic risk stratification requires external validation in independent cohorts.

Keywords: rate of glucose decline; insulin; hypoglycaemia; critical illness; glucose trajectory; intensive care unit; restrictive cubic spline

1 Introduction

Stress-induced hyperglycaemia is a common metabolic abnormality in critically ill patients. For patients with persistent or marked hyperglycaemia, insulin remains a key therapeutic modality for blood glucose management in the ICU [1-3]. However, the response to insulin in critically ill patients is highly heterogeneous[3,4], and treatment-related metabolic events, such as hypoglycaemia, may occur whilst hyperglycaemia is being controlled[4]. Consequently, how to reduce exposure to hyperglycaemia whilst avoiding excessive or rapid falls in blood glucose levels is a key challenge in the management of blood glucose in critically ill patients[4] . Stress-induced hyperglycaemia involves the combined action of multiple mechanisms[4,5]. Elevated levels of catecholamines, cortisol, inflammatory mediators and glucagon can enhance hepatic glucose output and induce peripheral insulin resistance [4,5];sepsis, nutritional support and glucocorticoid therapy can also further alter short-term glycaemic trajectories[1,5]. Consequently, hyperglycaemia observed in the ICU is often the result of the combined effects of disease severity, therapeutic interventions and monitoring strategies [1,4].

Previous ICU blood glucose studies have primarily focused on indicators such as absolute glucose levels, mean glucose levels, hypoglycaemic episodes, time within target range, and glucose variability. Whilst these indicators are valuable for describing the overall glycaemic status of critically ill patients, most reflect glucose levels already attained by the patient or the

degree of glucose dispersion over a period of time; they do not fully describe the direction and rate of change in blood glucose following specific therapeutic interventions. Large-scale randomised trials and systematic reviews have shifted the approach to ICU glycaemic management away from the notion that 'stricter is better' towards seeking a balance between hyperglycaemia control and the harms of hypoglycaemia [6,7]. Early single-centre randomised trials suggested that intensive insulin therapy might improve outcomes in certain ICU populations [5]; however, the large-scale NICE-SUGAR trial demonstrated that, compared with conventional control, strict glycaemic control may lead to a higher risk of mortality and more episodes of severe hypoglycaemia [1]. Current mainstream practice generally avoids the routine implementation of extremely strict glycaemic targets [8,9], as intensive control can increase the burden of hypoglycaemia[6,8], and hypoglycaemia itself is associated with mortality, neurological damage and increased treatment complexity [10].

In recent years, the concept of relative hypoglycaemia has further suggested that the same absolute blood glucose level may have different clinical implications in patients with different baseline glycaemic states. Assessing the relative degree of blood glucose reduction based on HbA1c or previous average blood glucose levels helps to understand glycaemic risk in critically ill patients from an individualised perspective[11,12]. However, relative hypoglycaemia primarily emphasises the extent to which blood glucose levels have fallen relative to a patient's previous or chronic glycaemic state; it is not equivalent to the kinetic characteristics of blood glucose decline per unit time following insulin treatment. Glucose variability primarily describes the degree of fluctuation or dispersion in blood glucose levels over a period of time [13,14]. Studies on relative hypoglycaemia and glycaemic variability collectively demonstrate that glycaemic risk cannot be explained solely by a single absolute threshold[13-15]. Relative hypoglycaemia emphasises a patient's prior glucose metabolic status[15], whilst glycaemic variability emphasises the dispersion or fluctuation of consecutive measurements[13,14]; together, they support the understanding of glycaemic abnormalities in critically ill patients based on time series rather than individual measurements [13-15].

In fact, previous multicentre ICU studies have already found that a larger decline in blood glucose levels and a faster rate of change prior to the onset of hypoglycaemia are associated with the severity of hypoglycaemia, suggesting that the kinetics of blood glucose changes may contain potential warning signals. Consequently, this study does not assume that the concept of 'rate of glucose decline' has never been investigated before; rather, it raises a distinct clinical question: following well-defined insulin therapy, can the rate of glucose decline within a fixed

early time window serve as a treatment response phenotype to characterise the risk of subsequent adverse metabolic events? Safety studies of insulin infusion regimens suggest [16] that hypoglycaemia during insulin therapy is associated with multiple factors, including nutritional interruption, sepsis, inotropic support, insulin exposure, and the need for close glucose monitoring [16-19];A post-treatment rate of blood glucose decline that is too rapid may be an observable phenotype emerging on the blood glucose trajectory as a result of the combined action of these factors, and thus holds significance as an early warning sign [17,19]; although previous protocol designs have incorporated the rate of blood glucose change as a basis for dose adjustment [19], its predictive value has not been systematically evaluated as a response phenotype within a fixed post-treatment time window.

This issue also differs from traditional glycaemic variability. Glycaemic variability primarily describes the degree of fluctuation or dispersion in blood glucose levels over a period of time, whereas the rate of post-treatment blood glucose decline possesses a clear direction, velocity and treatment-time anchor. Consequently, it may more closely reflect the patient's early dynamic response to insulin therapy.

Based on the above considerations, this study conceptualises early post-insulin GDR as a 'treatment-anchored dynamic glycaemic response phenotype'. We used the first insulin administration following hyperglycaemia in eligible patients as the index event, estimated GDR using longitudinal blood glucose measurements within a fixed 0–6-hour window thereafter, and adopted a 6-hour landmark design to temporally separate exposure calculation from the observation of subsequent outcomes.

We hypothesise that the relationship between GDR and the subsequent risk of hypoglycaemia is not a simple linear relationship, but may exhibit marked non-linearity and time-dependence; furthermore, this association may vary depending on whether insulin is administered subcutaneously or intravenously.Furthermore, this study further evaluates the association between GDR and severe hypoglycaemia, post-landmark hypokalaemia, and incident creatinine-based AKI, in order to systematically describe the relationship between early glucose decline kinetics and various metabolic safety outcomes.

2 Results

2.1 Study Population

The study flowchart is shown in Figure 1. Initially, there were 65,366 adult patients admitted to the ICU for the first time, of whom 21,578 experienced blood glucose levels ≥180 mg/dL during their ICU stay. Of these, 15,843 patients received insulin treatment within 24 hours of the qualifying hyperglycaemic episode. After applying a strict definition of the 'first insulin index', 12,924 patients were identified, of whom 12,450 were still alive and in the ICU at the 6-hour landmark following the index event. Ultimately, 10,933 patients with valid 0–6-hour

GDR data and for whom post-landmark blood glucose outcomes could be assessed were included in the primary analysis. In the primary analysis cohort: there were 811 events of blood glucose <70 mg/dL;244 cases of severe hypoglycaemia (<54 mg/dL).The complete-case analysis for hypokalaemia included 8,602 patients, of whom: 1,353 had K < 3.5 mmol/L; 201 had K < 3.0 mmol/L. The risk set for the primary analysis of incident creatinine-based AKI comprised 8,452 patients, of whom 1,438 developed AKI.

2.2 Baseline Characteristics

The median age in the primary analysis population was approximately 67 years, with males accounting for approximately 59.6 per cent. Compared with patients who did not experience hypoglycaemia after the landmark event, those who did experience hypoglycaemia had higher pre-index blood glucose levels: 245 (202–336) versus 223 (197–272) mg/dL, P < 0.001.The 0–6 h GDR was also significantly higher in patients who experienced hypoglycaemia: 14.8 (5.8–27.1) vs 9.0 (1.2–17.2) mg/dL/h, P < 0.001. The proportion of patients with diabetes was higher among those who experienced hypoglycaemia, as were the rates of vasopressor use and mechanical ventilation. There were significant differences between the groups in terms of insulin administration methods. Among patients who experienced hypoglycaemia, the proportion receiving IV insulin infusion was higher, whilst the proportion receiving SC prandial/correction insulin was lower. Furthermore, patients who experienced hypoglycaemia had lower pre-index MAP and GCS scores, suggesting certain differences between the two groups in terms of disease status and supportive care. Complete baseline characteristics are shown in Table 1.

2.3 GDR and primary hypoglycaemic outcomes

There was a significant overall association between GDR and post-landmark blood glucose levels <70 mg/dL. RCS overall test: $P = 3.16 \times 10^{-5}$. A marked non-linearity was also observed: P for non-linearity = 1.20×10^{-5}. More importantly, the association between GDR and hypoglycaemia varied significantly over time following the landmark: RCS × time interaction $P = 1.51 \times 10^{-10}$.Time-stratified linear analysis further revealed that, during the initial 0–6 hours following the landmark, each 10 mg/dL/h increase in GDR was associated with a higher hazard of hypoglycaemia: HR 1.009, 95% CI 1.004–1.014, P < 0.001. However, in subsequent time intervals, the strength and pattern of this association changed. Consequently, a single linear hazard ratio (HR) across the entire follow-up period cannot adequately characterise the exposure–response relationship between GDR and hypoglycaemia. The corresponding time-specific RCS curves are shown in Figure 2.

2.4 GDR and severe hypoglycaemia

A total of 244 cases of severe hypoglycaemia occurred among the 10,933 patients. There was a significant overall RCS association between GDR and severe hypoglycaemia: P = 0.002. There was also significant non-linearity: P for non-linearity < 0.001.Owing to the small number of severe hypoglycaemia events, a pre-specified reduced-order linear GDR-by-time interaction was used to assess temporal heterogeneity; the results remained statistically significant: P for

interaction = 0.007. Therefore, the findings on severe hypoglycaemia generally support those for the primary outcome, namely that the relationship between GDR and the risk of subsequent hypoglycaemia cannot simply be assumed to be a constant linear effect. The results are shown in Figure 4.

2.5 Effect Modification by Insulin Administration Method

A total of 9,967 patients were included in the main SC and IV insulin groups, with 735 major hypoglycaemic events occurring. The time-varying association between GDR and hypoglycaemia was significantly modified by insulin modality: 6-df RCS GDR × modality × time, P = 0.003.This suggests that the risk profile of GDR is not only related to the rate of glucose decline and time since the landmark, but also differs between patients receiving subcutaneous prandial/correction insulin and those receiving intravenous insulin infusion. The corresponding time-specific exposure–response curves are shown in Figure 3. It should be emphasised that this interaction does not prove that intravenous insulin itself leads to an increased risk of hypoglycaemia, as there are significant clinical selection factors and confounding by indication associated with the use of different insulin modalities.

2.6 GDR and hypokalaemia following the landmark event

In the analysis for K < 3.5 mmol/L, a total of 8,602 patients were included, with 1,353 events occurring. The linear model showed that for every 10 mg/dL/h increase in GDR: HR 0.990, 95% CI 0.984–0.995, P < 0.001.The overall RCS association was significant: P = 0.002. However, no clear non-linearity was observed: P for non-linearity = 0.636. At the same time, there was significant temporal heterogeneity: RCS × time, P < 0.001. For K < 3.0 mmol/L, a total of 201 events occurred. Linear model: HR 0.988, 95% CI 0.981–0.995, P = 0.002. Overall RCS association: P < 0.001. Non-linearity: P < 0.001. However, no clear temporal heterogeneity was observed: RCS × time, P = 0.151. Consequently, the two hypokalaemia thresholds exhibited different exposure–response characteristics: K < 3.5 mmol/L was characterised primarily by temporal heterogeneity without significant non-linearity, whilst K < 3.0 mmol/L exhibited marked non-linearity but no clear temporal heterogeneity.In the SC/IV modality analysis, the GDR × modality × time interaction for K < 3.5 mmol/L was P = 0.047; the corresponding three-way interaction for K < 3.0 mmol/L was P = 0.127. As this was an observational study, and hypokalaemia is influenced by monitoring, potassium supplementation and other treatments, an HR < 1 cannot be interpreted as indicating that a faster GDR has a protective effect against hypokalaemia. The results are shown in Figure 5 and Table2, Supplementary Table.

2.7 GDR and Incident Creatinine-Based AKI

The KDIGO-A primary analysis risk set included a total of 8,452 patients, of whom 1,438 developed incident creatinine-based AKI. No clear linear association was found between GDR and AKI: HR per 10 mg/dL/h = 0.998, 95% CI 0.991–1.006, P = 0.675.RCS overall association: P = 0.778. Non-linearity: P = 0.597. RCS × time: P = 0.736. Consequently, no consistent association between GDR and AKI was observed regardless of whether linear, non-linear or

time-varying models were used. Sensitivity analyses generally supported this negative finding. A P1–P99 winsorised analysis showed nominal statistical significance: HR 0.958, 95% CI 0.922–0.996, P = 0.029. However, this result was not replicated in the analyses using raw GDR, P1–P99 trimmed, ≥3 glucose measurements, KDIGO-B or KDIGO-C. Consequently, this isolated finding is insufficient to support a protective association between GDR and AKI. The results are shown in Figure 6 and Supplementary Table.

3 Discussion

This study established a timeline based on the initiation of insulin therapy and employed a 6-hour landmark design to temporally disentangle the early glycaemic dynamic response following the initiation of insulin therapy from subsequent clinical outcomes. The study yielded four main findings. Firstly, there was a clear non-linear and time-dependent association between GDR and subsequent hypoglycaemia. Second, this GDR–hypoglycaemia association was significantly modified by insulin modality. Third, GDR was also associated with post-landmark hypokalaemia; however, K < 3.5 mmol/L and K < 3.0 mmol/L exhibited different patterns of non-linearity and temporal heterogeneity. Fourth, no consistent association was observed between GDR and incident creatinine-based AKI, and multiple sensitivity analyses generally supported this negative finding. These results suggest that the information contained in GDR following insulin therapy cannot be simply summarised as 'the faster the decline, the higher the risk' or 'the slower the decline, the safer it is'; rather, it is more likely to represent a dynamic therapeutic response phenotype characterised by non-linearity, time dependence and treatment modality dependence.

This study represents a further extension of previous dynamic glucose studies, rather than a replacement for them. Previous multicentre ICU data have already demonstrated that the magnitude and rate of glucose decline prior to the onset of hypoglycaemia increase with the severity of hypoglycaemia [20], indicating that antecedent glucose kinetics possess clinical significance in their own right.Subsequent studies on relative hypoglycaemia have further demonstrated that a marked decline relative to the patient's previous glucose status is associated with subsequent absolute hypoglycaemia and other adverse outcomes [11,12]. Therefore, the innovation of this study does not lie in being the first to propose that 'the rate of glucose decline is associated with hypoglycaemia'.This study addresses a different question: following a clearly defined insulin treatment event, can the longitudinal rate of glucose decline within a fixed early time window serve as a dynamic treatment response phenotype to characterise the risk of subsequent hypoglycaemia and other metabolic events? Compared with previous studies, this study has three key distinctions. Firstly, this study employs explicit treatment anchoring. The starting point of exposure is not ICU admission, nor is it the retrospective identification of precursor changes following a hypoglycaemic event that has already occurred; rather, it is the actual index insulin treatment. Secondly, this study employs explicit temporal separation. GDR is estimated only within 0–6 hours following the index event, whilst outcomes are observed only from the 6-hour landmark onwards; this reduces temporal overlap between exposure and outcome definitions and provides a clear, landmark-based conditional interpretation of risk estimates [21].Thirdly, this study further characterised the exposure–response architecture of the GDR–hypoglycaemia relationship. The results indicate

that this relationship is not a simple linear association, but is characterised by significant non-linearity, strong temporal heterogeneity and insulin-modality effect modification. Therefore, the core innovation of this study is more accurately described as: treating early GDR following insulin therapy as a treatment-anchored dynamic glycaemic response phenotype, and revealing its non-linear, time-dependent and treatment-modality-dependent association with subsequent hypoglycaemia.

Traditional ICU glycaemic metrics predominantly describe the patient's glycaemic 'state'. For example, absolute glucose indicates the blood glucose level at a specific point in time; mean glucose describes average exposure over a period of time; glycaemic variability describes the degree of dispersion or fluctuation in blood glucose levels [13]; whilst relative hypoglycaemia emphasises the degree of decline relative to the patient's chronic glycaemic baseline [15].Previous studies have shown that the amplitude of fluctuations and the irregularity of patterns in the glucose time series of critically ill patients change with the course of the illness and insulin therapy, suggesting that dynamic glucose metrics can provide information that single glucose readings cannot [22]. GDR addresses a different issue. It emphasises the rate at which a patient's blood glucose is falling following the administration of insulin. Consequently, GDR incorporates information relating to both treatment and the patient's response. Even with a similarly high initial blood glucose level, one patient may experience a slow decline over several hours whilst another experiences a rapid decline; their subsequent risk of hypoglycaemia may therefore differ. Furthermore, the GDR should not be simply regarded as a surrogate for insulin dose. Its formation may be influenced by a combination of factors, including baseline blood glucose, insulin administration route, insulin sensitivity, endogenous glucose production, nutritional intake, disease severity and other supportive treatments [23,24]. Consequently, we prefer to view the GDR as a dynamic treatment-response phenotype rather than an isolated laboratory biomarker.

A key finding was the marked temporal heterogeneity of the GDR-hypoglycaemia association (RCS-by-time interaction P = 1.51 x 10^-10). During the first 0-6 h after the landmark, each 10 mg/dL/h increase in GDR was associated with a higher hypoglycaemia hazard; this association changed in later intervals. This pattern is consistent with evidence that glycaemic variability increases before hypoglycaemia in critically ill patients [25].A conventional proportional-hazards model could obscure this early association by averaging effects across follow-up. GDR may therefore represent a short-term dynamic risk signal rather than a fixed patient characteristic [26]. If externally validated, its value may lie in estimating whether the current glucose trajectory indicates an increased risk of hypoglycaemia in the coming hours. The risk of hypoglycaemia also varies with disease severity, mechanical ventilation and renal replacement therapy, supporting a dynamic rather than fixed interpretation of risk [26].

This study found that insulin modality exerts a significant effect modification on the association between GDR and hypoglycaemia. Subcutaneous (SC) and intravenous (IV) insulin differ markedly in terms of administration route, pharmacokinetics, clinical settings and monitoring frequency [19]. Consequently, even when the same GDR is observed, the underlying therapeutic context may be entirely different.Among ICU patients receiving intravenous insulin infusion, higher infusion rates are associated with an increased risk of

hypoglycaemia [27], suggesting that the intensity of insulin administration itself may influence the risk of hypoglycaemia. This finding further illustrates that the clinical significance of GDR cannot be interpreted in isolation from the therapeutic context in which it arises. However, it must be emphasised that this study cannot draw a causal conclusion that 'IV insulin leads to a higher risk of hypoglycaemia'. The mode of insulin administration was not randomly assigned; IV insulin is often used in patients with varying disease severity, glycaemic control targets and clinical conditions. Although the model has been adjusted for multiple baseline covariates, confounding by indication and residual confounding cannot be completely ruled out. Therefore, the modality interaction is best interpreted as follows: the risk information conveyed by GDR is context-dependent. When interpreting GDR clinically, process factors such as infusion regimens, frequent blood glucose monitoring, nutritional support and hypoglycaemia prevention measures should also be taken into account [28].

This study also observed an association between GDR and post-landmark hypokalaemia, although the pattern differed markedly from that seen with hypoglycaemia. Insulin promotes the intracellular transport of potassium ions, and this effect often occurs in parallel with changes in glucose metabolism; however, in the ICU setting, serum potassium trajectories are also jointly influenced by potassium replacement strategies, diuretics, renal function, acid-base status, gastrointestinal losses and the timing of blood sampling [29].Consequently, the statistical association between GDR and hypokalaemia has a plausible biological basis [30], but it cannot be inferred from this that the rate of blood glucose decline itself is the direct cause of hypokalaemia. $K < 3.5$ mmol/L is characterised primarily by an overall association and significant temporal heterogeneity, whilst lacking clear non-linearity. In contrast, $K < 3.0$ mmol/L exhibits a marked non-linear association, but there is insufficient evidence to support temporal heterogeneity. This discrepancy suggests that potassium outcomes of varying severity may have different clinical and physiological determinants. However, particular caution is required when interpreting results showing an $HR < 1$ in linear models. Firstly, this study evaluated post-landmark hypokalaemia, and it was not possible to strictly confirm that this represented de novo hypokalaemia in all patients. Secondly, serum potassium levels are influenced by a combination of baseline potassium, potassium replacement therapy, renal function, acid-base status, nutrition and other treatments. Furthermore, the measurement of potassium levels is itself part of the clinical observation process; patients at higher risk may undergo more frequent testing. Therefore, the results of this study cannot be interpreted as indicating that a more rapid GDR prevents hypokalaemia. A more reasonable conclusion is that there is a complex and time-dependent statistical association between early glucose dynamics and subsequent potassium trajectories, the specific mechanisms of which require further investigation.

Unlike hypoglycaemia and potassium outcomes, this study did not find a consistent association between GDR and incident creatinine-based AKI. The hazard ratio (HR) in the primary analysis was close to 1, and the tests for overall RCS, non-linearity and RCS×time were all non-significant. This negative result is also significant. If GDR were merely a non-specific surrogate marker of disease severity or overall poor prognosis, one might expect it to exhibit similar associations with a variety of adverse outcomes. However, this was not the case in this study. Hypoglycaemia exhibited a strong non-linear/time-varying association, whilst AKI

remained generally negative across various analytical strategies. This suggests that the information contained within GDR may be more closely related to short-term glycaemic/metabolic response rather than serving as a generalised risk indicator for adverse outcomes across all organs. It is worth noting that a nominal P-value of 0.029 was observed in the winsorised sensitivity analysis; however, this result was not replicated in the raw, trimmed, ≥3 measurements, KDIGO-B or KDIGO-C analyses. Therefore, this isolated finding should not be interpreted as a protective association.

The present study does not currently support the immediate establishment of a fixed GDR cut-off for clinical decision-making. Instead, the findings suggest three key directions for further investigation. Firstly, the rate of glucose decline may provide information beyond that offered by absolute glucose levels. For ICU patients receiving insulin therapy, knowledge of the current glucose value alone may be insufficient to fully characterise the risk of recent hypoglycaemia; the rate of recent glucose change may be equally important. Secondly, this risk information is time-dependent. The same GDR value cannot be assumed to carry exactly the same risk implications across different post-treatment intervals. Thirdly, the interpretation of the GDR must take into account the insulin administration route. Patients receiving subcutaneous (SC) insulin should not be assessed using exactly the same exposure–response framework as those receiving intravenous (IV) insulin. Consequently, a tool with genuine clinical translational value in the future may not be a simple formula such as 'GDR > a fixed value = high risk', but rather a comprehensive model: current blood glucose level + recent blood glucose trajectory + insulin administration route + baseline clinical status + time to treatment → risk of hypoglycaemia in the coming hours. This study provides observational evidence for this dynamic risk prediction framework; however, it is not yet sufficient to establish treatment guidelines that directly guide insulin dose adjustments. Previous clinical practice studies have shown that hypoglycaemic events can be significantly reduced under conservative targeting and standardised intravenous insulin protocols [31].This evidence indirectly suggests that the value of the GDR prediction tool lies more in its integration into such effective protocols, serving as a supplementary layer of risk warning, whilst its role independent of clinical protocols is relatively limited.

Strengths include anchoring the analysis to index insulin treatment, using a 6-h landmark design to separate exposure assessment from outcome follow-up, and estimating GDR from multiple glucose measurements rather than a single pre/post-treatment difference. We retained raw GDR in primary analyses and tested alternative exposure handling strategies. Pre-specified spline knots and reference values enabled systematic assessment of non-linearity, temporal heterogeneity and insulin-modality interaction across hypoglycaemia, potassium outcomes and creatinine-based AKI.

This study has several important limitations. This retrospective observational study cannot establish causality. Insulin modality was not randomly assigned, leaving possible confounding by indication and residual confounding despite covariate adjustment. Monitoring frequency was also non-random and may have introduced observation-process bias. A linear 0–6-h slope cannot capture complex trajectories such as decline, plateau and rebound. Post-landmark hypokalaemia may have been affected by testing frequency and potassium replacement, and

AKI was defined using creatinine criteria without urine output or renal replacement therapy. Finally, this single-database study lacks external validation; variations in patient populations, insulin protocols and monitoring practices may limit generalisability. Secondary outcomes, marginal modality interactions and isolated sensitivity-analysis findings require cautious interpretation.

Among hyperglycaemic ICU patients receiving insulin, early glucose decline rate was non-linearly and time-dependently associated with subsequent hypoglycaemia, with patterns differing by insulin administration route. Associations with post-landmark hypokalaemia were also observed, whereas no consistent association was found with incident creatinine-based AKI. These findings indicate that early glucose dynamics may contribute to short-term metabolic risk assessment; their predictive value and clinical utility require external validation.

4 Methods

4.1 Data Sources and Study Design

This study conducted a retrospective cohort study using the MIMIC-IV database, a de-identified intensive care database containing structured information on hospitalisation, ICU stays, laboratory tests and medication [32]. This study utilised de-identified secondary data; the research report adheres to the guidelines for reporting observational studies [33,34]. Variable extraction, the temporal definitions of exposures and outcomes, the handling of missing data, and pre-specified sensitivity analyses are all traceable within the analysis code to enhance the study's reproducibility. The study population comprised adult ICU patients. The study first identified patients who developed eligible hyperglycaemia during their ICU stay and further determined the actual insulin treatment they subsequently received. To minimise correlation and selection bias arising from multiple ICU admissions by the same patient, the study cohort was constructed according to predefined rules. This study uses clearly defined insulin treatment events, rather than the time of ICU admission, as the core anchor points of the study timeline. The overall study design comprises three consecutive phases: index insulin → 0–6 h GDR exposure window → 6 h landmark → subsequent outcome follow-up. This landmark design ensures temporal separation between the definition of exposure and the observation of outcomes.

4.2 Definitions of Hyperglycaemia and Index Insulin

Eligible hyperglycaemia is defined as a blood glucose level of ≥180 mg/dL during the ICU stay. Following the occurrence of eligible hyperglycaemia, insulin treatment actually administered within the subsequent 24 hours is identified, and the first eligible insulin treatment is designated as the 'index insulin' according to predefined rules. Intravenous insulin is identified primarily on the basis of actual ICU administration records; subcutaneous insulin is identified on the basis of actual medication administration records, rather than solely on the basis of prescribing orders.

4.3 Definition of GDR

The primary exposure was the glucose decline rate (GDR) within 0–6 hours following the index insulin administration. For each patient, the slope of glucose change over time was estimated using an intra-patient ordinary least squares linear regression, with all available glucose measurements within this time window as the dependent variable and the measurement time as the independent variable; the direction of glucose decline was defined as positive, such that a larger positive GDR indicates a faster rate of glucose decline per unit of time. The primary analysis utilised raw continuous GDR values; no cut-off points were arbitrarily defined based on the outcome, nor were outliers removed from the primary analysis. Sensitivity analyses were further conducted using P1–P99 winsorisation, P1–P99 trimming, and restricting the analysis to patients with at least three valid blood glucose measurements within the 0–6 h window, to assess the robustness of the results to different exposure estimation methods.

4.4 Landmark Design and Follow-up

A 6-hour landmark design was adopted. The key feature of the landmark design is that only patients who remain in the at-risk population at the predefined landmark time point are included in the analysis, and exposure is defined using only information available prior to the landmark. Events occurring during the exposure calculation period are therefore not misclassified as subsequent outcomes, and the time-dependent bias and exposure–outcome time overlap commonly observed in time-dependent exposure analyses are consequently reduced [21,35]. GDR exposure was determined solely on the basis of data from 0–6 hours following the index insulin dose. Patients were eligible for inclusion in the landmark cohort only if they were still alive and in the ICU at the 6-hour landmark time point. All primary outcomes were observed from the landmark time point onwards. The follow-up endpoint was defined as 24 hours after the landmark or the time of discharge from the ICU, whichever occurred first. This design avoids including glucose changes occurring within the GDR calculation window as part of subsequent outcomes, thereby enhancing the clarity of the temporal sequence between exposure and outcome.

4.5 Study Outcomes

4.5.1 Primary Outcomes

The primary outcome is hypoglycaemia after the landmark: blood glucose <70 mg/dL.

4.5.2 Severe Hypoglycaemia

Severe hypoglycaemia is defined as: blood glucose <54 mg/dL. (In this study, this is defined as blood glucose <54 mg/dL, corresponding to IHSG level 2 clinically significant hypoglycaemia; it does not refer to level 3 severe hypoglycaemic events requiring assistance from others to recover.)

4.5.3 Hypokalaemia

Hypokalaemia outcomes include: K < 3.5 mmol/L; severe hypokalaemia: K < 3.0 mmol/L. As it is not possible to strictly confirm the absence of hypokalaemia prior to the landmark event

in all patients, the term ‘post-landmark hypokalaemia’ is used consistently throughout the text, rather than referring to it as ‘incident hypokalaemia’ in the strict sense.

4.5.4 Acute Kidney Injury

The primary analysis of AKI used the pre-specified KDIGO-A reference-creatinine definition. Patients who met the corresponding creatinine-based AKI criteria before or at the landmark were excluded from the risk set. Because serum creatinine is influenced by volume status, muscle mass, and measurement frequency [36,37], this creatinine-based definition should be interpreted as an operational proxy for changes in renal function. As urine output and renal replacement therapy criteria were not incorporated [38], the outcome was termed “incident creatinine-based AKI” rather than the complete KDIGO AKI phenotype.

4.6 Covariates

Adjustment variables were pre-specified based on clinical relevance and data completeness. The primary models included age, sex, pre-index blood glucose, diabetes, chronic kidney disease, sepsis, pre-index use of vasoactive agents, mechanical ventilation, glucocorticoid use, time from ICU admission to index insulin, and insulin administration method. The hypokalaemia model further enforced adjustment for baseline potassium. Variables such as lactate and GCS, due to their high rates of missing data, were not included as core adjustment variables to maintain the sample size for the primary analysis; instead, they were used in extended models or for sensitivity analyses. Post-landmark monitoring frequency was not included in the primary models as a general baseline confounder, as post-treatment monitoring behaviour itself may be influenced by patient condition, treatment modality and early treatment response.

4.7 Statistical Analysis

Continuous variables were presented as the median and interquartile range according to their distribution, whilst categorical variables were presented as frequencies and percentages. Cox proportional hazards models were primarily used to assess the association between GDR and subsequent time-to-event outcomes, with robust standard errors applied to account for clustering at the stay_id level. Restricted cubic splines [39] were employed to evaluate potential non-linear exposure–outcome relationships. The RCS nodes were pre-fixed at the 5th, 35th, 65th and 95th percentiles of the raw GDR distribution: −13.743, 5.028, 13.909 and 42.557 mg/dL/h. The reference value was the median GDR: 9.388 mg/dL/h. The plot range was restricted to the 1st–99th percentiles of the GDR to minimise the influence of extreme outlier data on the plot scale; however, the main model retained the full set of original GDR data. To assess temporal heterogeneity, the follow-up period after the landmark event was divided into: 0–6 h, >6–12 h and >12–24 h. The model utilised baseline hazards stratified by time band. For the primary hypoglycaemia outcome, a 6-degree-of-freedom joint RCS-by-time interaction test was employed [40]. Due to the relatively small number of events, a simpler 2-degree-of-freedom linear GDR-by-time interaction was used to assess temporal heterogeneity for severe hypoglycaemia [40]. For hypokalaemia and AKI, time-dependent changes were primarily

assessed using RCS-by-time interaction tests. Additionally, the effect modification of insulin modality was pre-specified. The primary comparison was between subcutaneous (SC) prandial/correction insulin and intravenous (IV) insulin infusion; hierarchical interaction models were employed to incorporate the corresponding main effects, two-way interactions and GDR-by-modality-by-time interactions. Sensitivity analyses included P1–P99 winsorisation and P1–P99 trimming of the GDR, restriction to patients with at least three blood glucose measurements, and the use of alternative KDIGO-B and KDIGO-C reference-creatinine definitions for AKI. All statistical tests were two-sided. Given that the study objectives focused on non-linear and time-varying relationships, the results were interpreted based on the combined effect estimates, 95% CIs, RCS curves, interaction tests and the consistency across different sensitivity analyses, rather than relying solely on individual P-values to determine clinical significance.

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Author Contributions

Zimeng Guo, Xiang Qi, and Yidan Zhang contributed equally to this work. Zimeng Guo: Conceptualization, Methodology, Software, Formal analysis, Data curation, Visualization, and Writing (original draft). Xiang Qi: Methodology, Validation, Formal analysis, and Writing (review and editing). Yidan Zhang: Data curation, Validation, Visualization, and Writing

(review and editing). Shanshan Pang: Conceptualization, Supervision, Project administration, and Writing (review and editing). All authors contributed to the interpretation of the findings, reviewed the manuscript, and approved the final version.

Data availability

The data used in this study are available from the MIMIC-IV database on PhysioNet. Access is restricted to credentialed users who complete the required data-use agreement and training. The data are not publicly redistributed by the authors because of the terms governing access to MIMIC-IV. The code used for data extraction and statistical analysis is available from the corresponding author upon reasonable request.

Competing interests

The author(s) declare no competing interests.

Ethics approval and consent to participate

This study used de-identified data from the MIMIC-IV database. The creation of the MIMIC-IV database was approved by the Institutional Review Boards of the Beth Israel Deaconess Medical Center (protocol No. 2001-P-001699) and the Massachusetts Institute of Technology (protocol No. 0403000206). The requirement for individual informed consent was waived because the data were de-identified.

Consent for publication

Not applicable.

Figure legends

Figure 1. Study cohort construction and analysis populations for different outcomes

Flowchart showing the selection of adult ICU patients from the MIMIC-IV database. Patients with blood glucose ≥180 mg/dL who subsequently received insulin were screened. The first eligible insulin administration was defined as the index event. Patients who remained alive and in the ICU at the 6-hour landmark and had valid glucose measurements during the 0–6-hour exposure window were included in the primary analysis. The final cohort comprised 10,933 patients.

Figure 2. Time-varying non-linear association between early glucose decline rate and post-landmark hypoglycaemia (<70 mg/dL)

Restricted cubic spline curves showing the association between early glucose decline rate (GDR) during the 0–6-hour period after index insulin administration and subsequent hypoglycaemia (blood glucose <70 mg/dL) across three post-landmark intervals: 0–6

hours, >6–12 hours and >12–24 hours. The curves illustrate the non-linear and time-dependent relationship between GDR and hypoglycaemia risk. Shaded areas represent 95% confidence intervals.

Figure 3. Effect modification by insulin administration route of the time-varying association between GDR and post-landmark hypoglycaemia

Time-specific restricted cubic spline curves showing the association between early glucose decline rate and subsequent hypoglycaemia according to insulin administration route. The analysis compares subcutaneous prandial or correction insulin with intravenous insulin infusion across the post-landmark follow-up intervals. The results indicate that the exposure–response relationship varied according to both insulin modality and time since the landmark. Shaded areas represent 95% confidence intervals.

Figure 4. Association between early glucose decline rate and post-landmark severe hypoglycaemia (<54 mg/dL)

Restricted cubic spline analysis of the association between early glucose decline rate during the 0–6-hour exposure window and subsequent severe hypoglycaemia, defined as blood glucose <54 mg/dL. The figure presents the overall exposure–response relationship and its temporal variation during follow-up. Shaded areas represent 95% confidence intervals.

Figure 5. Time-varying association between early glucose decline rate and post-landmark hypokalaemia

Restricted cubic spline analyses showing the associations between early glucose decline rate and post-landmark hypokalaemia defined as serum potassium <3.5 mmol/L or <3.0 mmol/L. The analyses assess potential non-linearity, temporal heterogeneity and modification by insulin administration route. Because potassium monitoring and replacement therapy may influence the observed outcomes, the associations should not be interpreted as causal or as evidence of a protective effect.

Figure 6. Association between early glucose decline rate and incident creatinine-based acute kidney injury, with sensitivity analyses

Restricted cubic spline analysis of the association between early glucose decline rate and incident creatinine-based acute kidney injury after the 6-hour landmark. The primary analysis used the pre-specified KDIGO-A reference-creatinine definition. No consistent linear, non-linear or time-varying association was observed. Shaded areas represent 95% confidence intervals.

Tables

Table 1. Baseline characteristics of the primary analysis cohort according to post-landmark hypoglycaemia status

Baseline demographic characteristics, clinical conditions, laboratory measurements, treatments and insulin administration routes of patients with and without post-landmark hypoglycaemia. Continuous variables are presented as medians with interquartile ranges, and categorical variables as numbers and percentages. GDR was calculated from glucose measurements obtained during the 0–6-hour period after index insulin administration.

Characteristic	Overall (N=10,933)	No hypoglycaemia (N=10,122)	Hypoglycaemia <70 mg/dL (N=811)	P value	Available N
Demographics					
Age, years	67 (57–76)	67 (57–76)	67 (56–76)	0.416	
Sex, n (%)				0.044	
Female	4,421 (40.4)	4,066 (40.2)	355 (43.8)		
Male	6,512 (59.6)	6,056 (59.8)	456 (56.2)		
Baseline glycaemic characteristics					
Pre-index glucose, mg/dL	224 (197–276)	223 (197–272)	245 (202–336)	<0.001	
Comorbidities					
Diabetes mellitus, n (%)	7,698 (70.4)	7,080 (69.9)	618 (76.2)	<0.001	
Chronic kidney disease, n (%)	2,878 (26.3)	2,659 (26.3)	219 (27.0)	0.648	
Sepsis, n (%)	2,159 (19.7)	2,001 (19.8)	158 (19.5)	0.844	
Pragmatic Charlson comorbidity score	2 (1–3)	2 (1–3)	2 (0–3)	0.156	
Baseline laboratory and physiological characteristics					
Potassium, mmol/L	4.2 (3.8–4.7)	4.2 (3.8–4.7)	4.3 (3.8–4.8)	0.339	9,207
Creatinine, mg/dL	1.1 (0.8–1.7)	1.1 (0.8–1.7)	1.2 (0.9–1.8)	<0.001	10,457
Lactate, mmol/L	2.4 (1.7–3.7)	2.4 (1.6–3.6)	2.8 (1.8–5.0)	<0.001	5,752
Minimum MAP over the preceding 6 hours, mmHg	68 (60–78)	68 (61–78)	66 (58–76)	<0.001	10,221
GCS prior to the index	11 (6–15)	11 (6–15)	8 (3–14)	<0.001	9,139
Pre-index treatment and organ support					
Use of vasopressors in the preceding 6 hours, n (%)	3,749 (34.3)	3,377 (33.4)	372 (45.9)	<0.001	
Mechanical ventilation, n (%)	5,688 (52.0)	5,196 (51.3)	492 (60.7)	<0.001	
Systemic corticosteroid administration in the preceding 24 hours, n (%)	991 (9.1)	948 (9.4)	43 (5.3)	<0.001	
Time from ICU admission to insulin index, h	7.9 (3.7–18.7)	8.2 (3.8–19.6)	5.6 (2.4–11.3)	<0.001	
Insulin modality					
Insulin treatment group, n (%)				<0.001	
Subcutaneous prandial/correction	6,327 (57.9)	6,086 (60.1)	241 (29.7)		
Intravenous infusion	3,640 (33.3)	3,146 (31.1)	494 (60.9)		
Other	966 (8.8)	890 (8.8)	76 (9.4)		
Early glycaemic response (0–6 h)					
Glucose decline rate, mg/dL/h	9.4 (1.6–18.0)	9.0 (1.2–17.2)	14.8 (5.8–27.1)	<0.001	

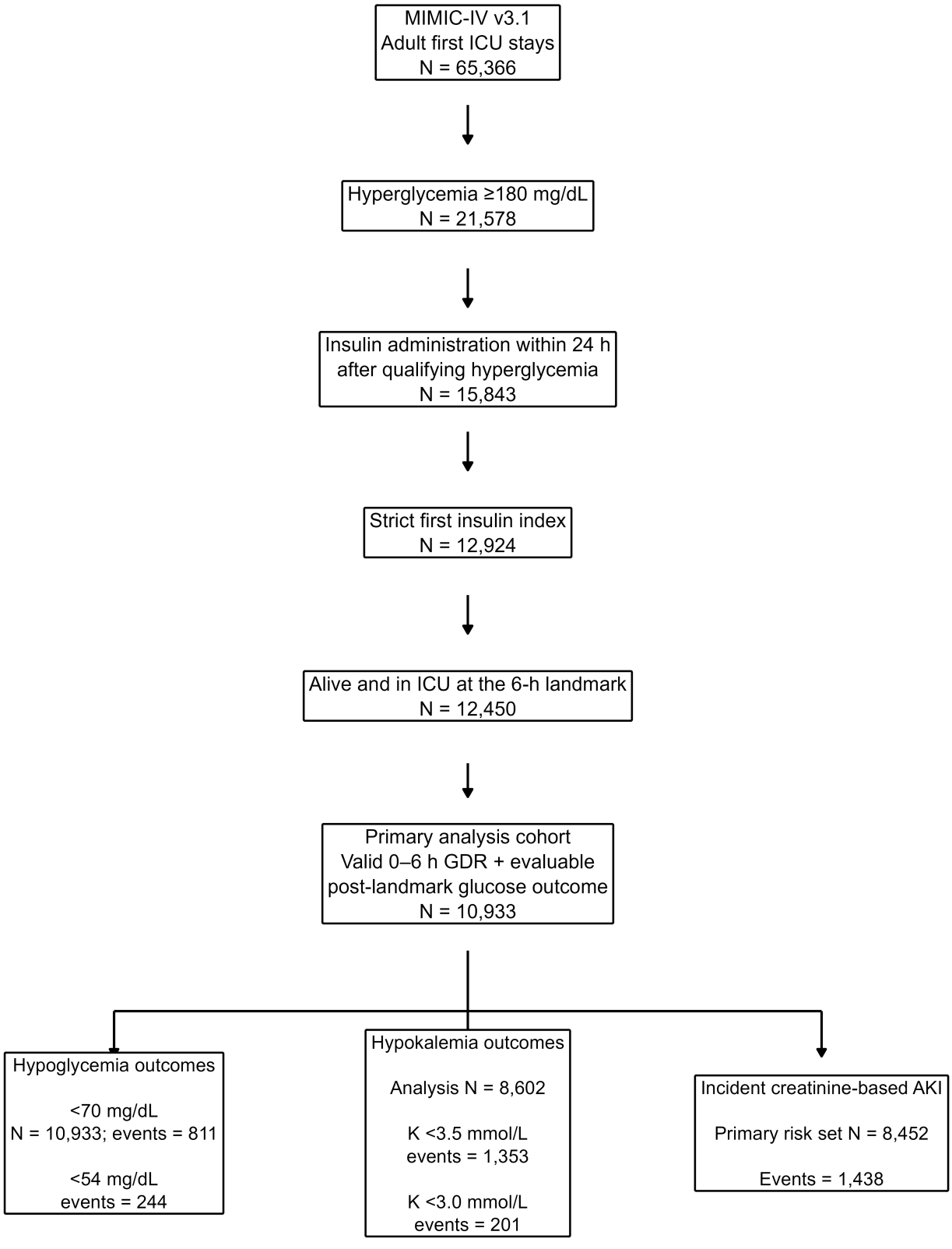
Table 2. Associations of early glucose decline rate (GDR) with post-landmark hypoglycaemia, hypokalaemia, and acute kidney injury

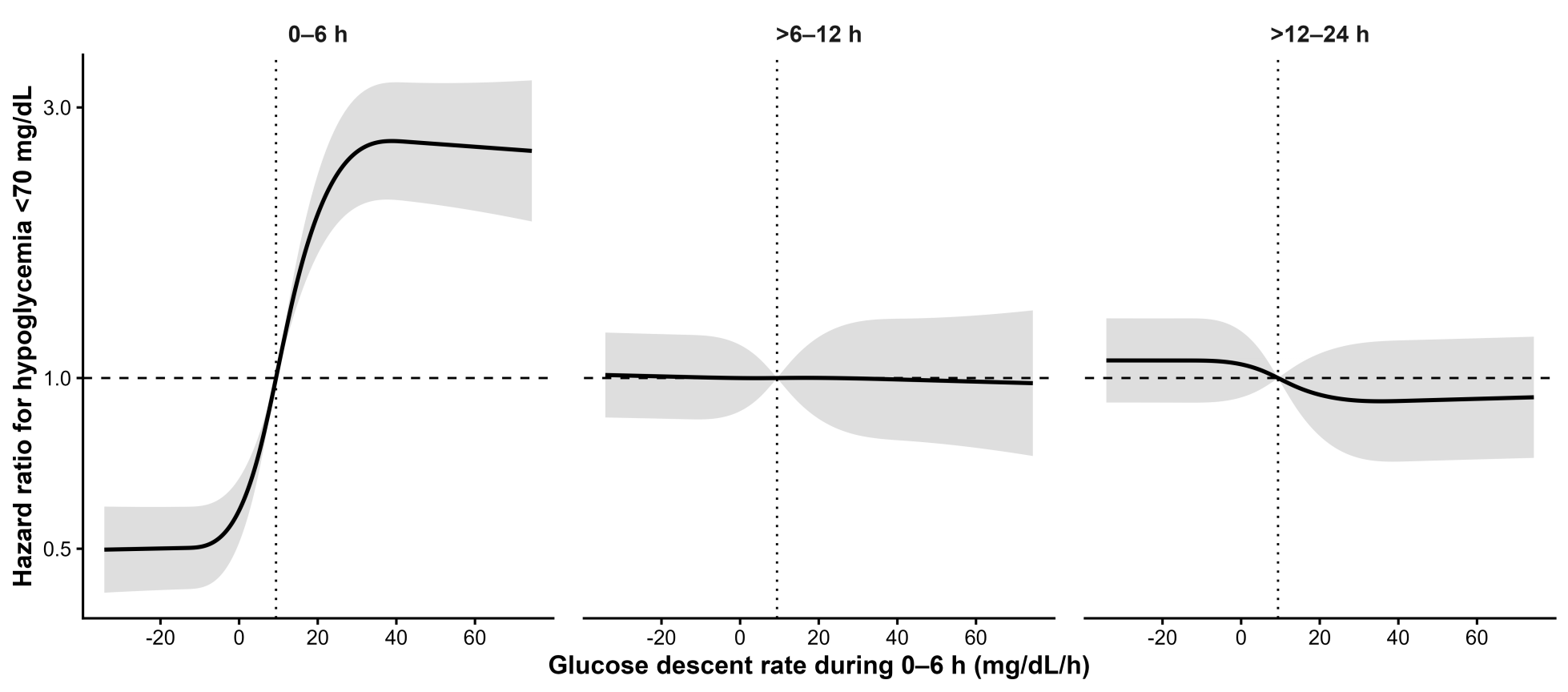
Associations between early glucose decline rate and subsequent hypoglycaemia or severe hypoglycaemia. Results are presented as hazard ratios with 95% confidence intervals from linear and restricted cubic spline models. Analyses evaluate overall associations, non-linearity,

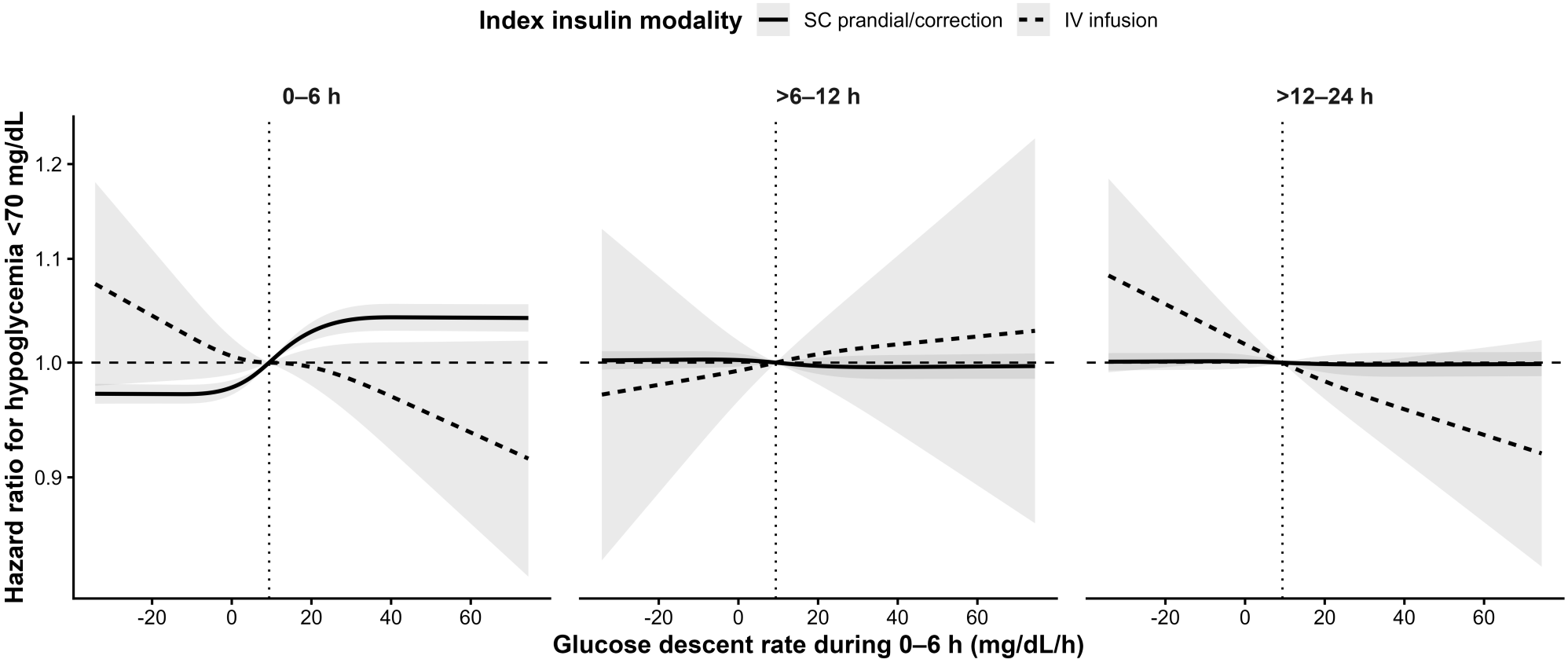
temporal heterogeneity and effect modification by insulin administration route.

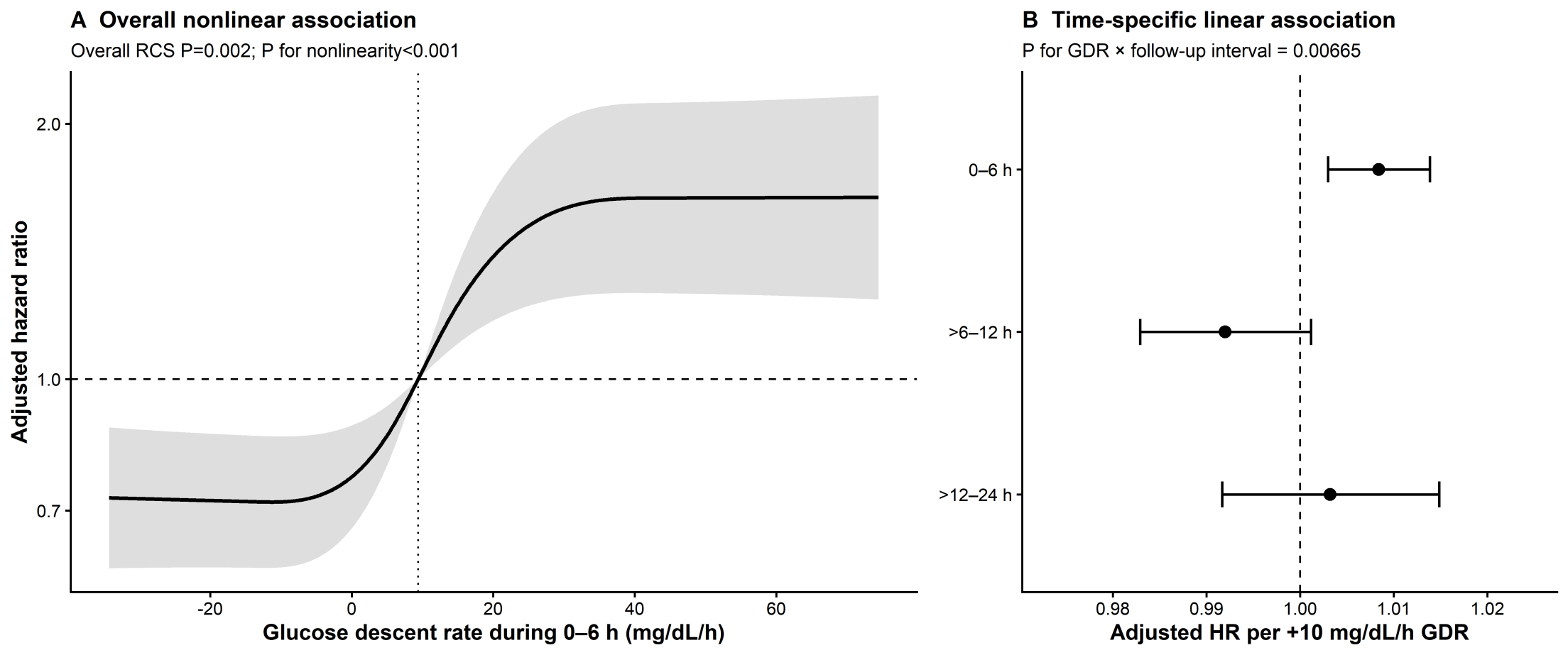
Outcome	N	Events	Linear HR per +10 mg/dL/h GDR (95% CI)	Linear P value	Overall RCS P-value	RCS non-linearity P-value	GDR × follow-up time P-value	Time-interaction form
Post-landmark hypoglycaemia <70 mg/dL	10,933	811	1.009 (1.004–1.014)	<0.001	<0.001	<0.001	<0.001	RCS, 6 df
Post-landmark clinically significant hypoglycaemia <54 mg/dL	10,933	244	1.005		0.002	<0.001	0.007	Linear, 2 df
Post-landmark hypokalaemia <3.5 mmol/L	8602	1353	0.990 (0.984–0.995)	<0.001	0.002	0.636	<0.001	RCS, 6 df
Post-landmark severe hypokalaemia <3.0 mmol/L	8602	201	0.988 (0.981–0.995)	0.002	<0.001	<0.001	0.151	RCS, 6 df
Incident creatinine-based AKI	8,452	1,438	0.998 (0.991–1.006)	0.675	0.778	0.597	0.736	RCS, 6 df

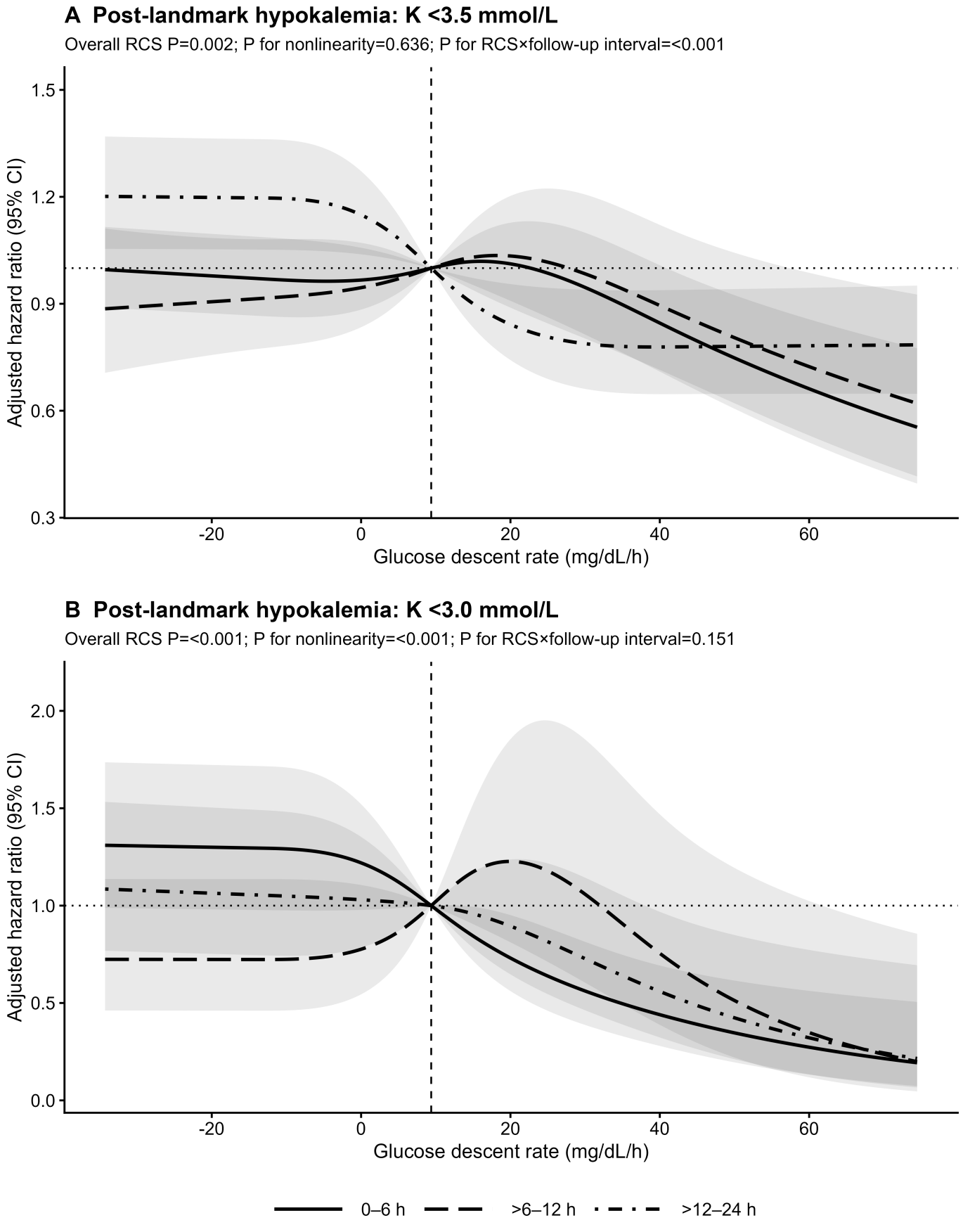
Study cohort and analysis populations

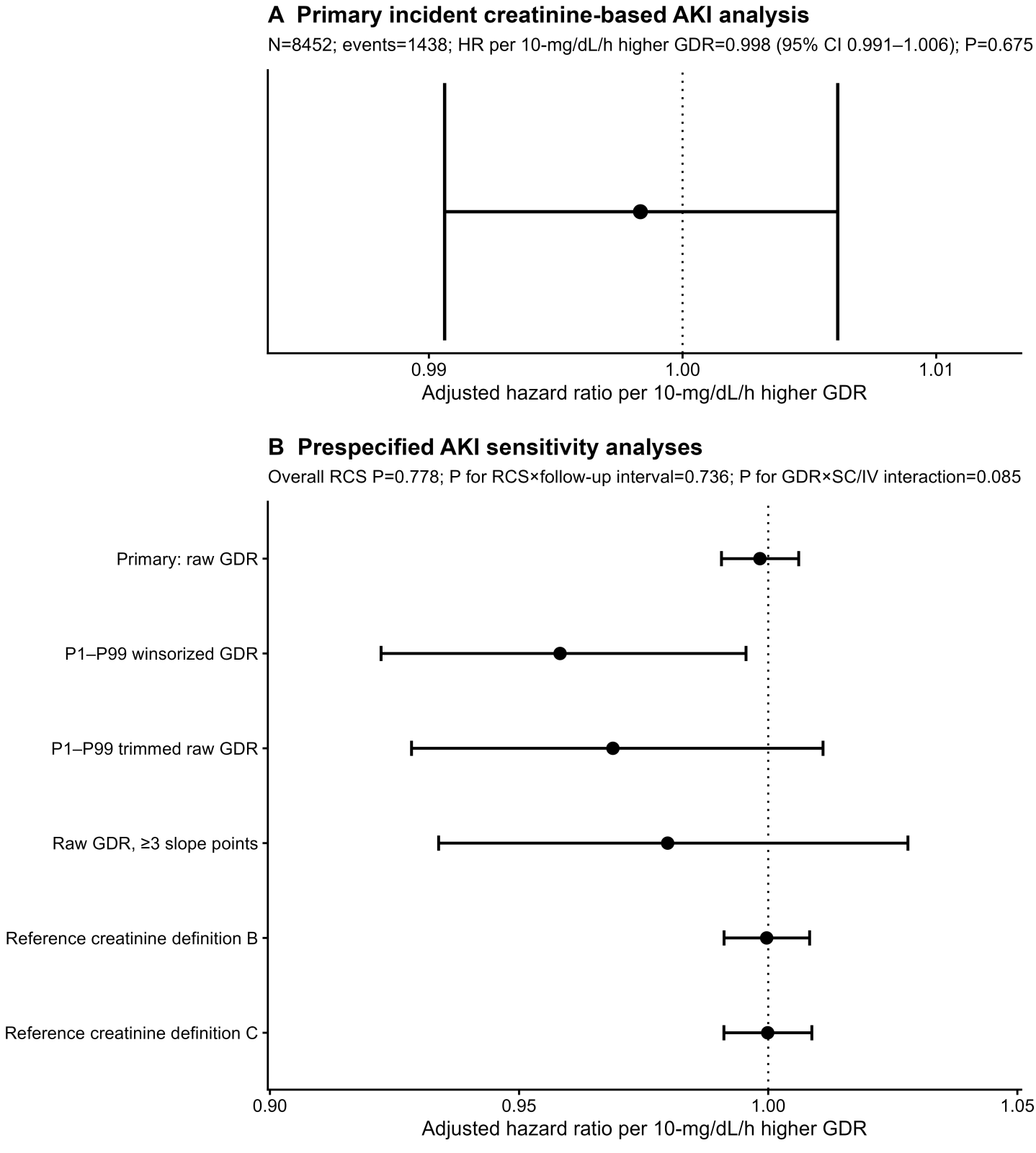



0–6 h
>6–12 h
>12–24 h
Hazard ratio for hypoglycemia <70 mg/dL
3.0
1.0
0.5
-20
0
20
40
60
Glucose descent rate during 0–6 h (mg/dL/h)


Index insulin modality
SC prandial/correction
IV infusion
0–6 h
>6–12 h
>12–24 h
Hazard ratio for hypoglycemia <70 mg/dL
1.2
1.1
1.0
0.9
-20
0
20
40
60
Glucose descent rate during 0–6 h (mg/dL/h)


A Overall nonlinear association
Overall RCS P=0.002; P for nonlinearity<0.001
Adjusted hazard ratio
2.0
1.0
0.7
-20
0
20
40
60
Glucose descent rate during 0–6 h (mg/dL/h)
B Time-specific linear association
P for GDR × follow-up interval = 0.00665
0–6 h
>6–12 h
>12–24 h
0.98
0.99
1.00
1.01
1.02
Adjusted HR per +10 mg/dL/h GDR


A Post-landmark hypokalemia: K <3.5 mmol/L
Overall RCS P=0.002; P for nonlinearity=0.636; P for RCS×follow-up interval=<0.001
Adjusted hazard ratio (95% CI)
1.5
1.2
0.9
0.6
0.3
-20
0
20
40
60
Glucose descent rate (mg/dL/h)
B Post-landmark hypokalemia: K <3.0 mmol/L
Overall RCS P=<0.001; P for nonlinearity=<0.001; P for RCS×follow-up interval=0.151
Adjusted hazard ratio (95% CI)
2.0
1.5
1.0
0.5
0.0
-20
0
20
40
60
Glucose descent rate (mg/dL/h)
0–6 h
>6–12 h
>12–24 h


A Primary incident creatinine-based AKI analysis
N=8452; events=1438; HR per 10-mg/dL/h higher GDR=0.998 (95% CI 0.991–1.006); P=0.675
0.99
1.00
1.01
Adjusted hazard ratio per 10-mg/dL/h higher GDR
B Prespecified AKI sensitivity analyses
Overall RCS P=0.778; P for RCS×follow-up interval=0.736; P for GDR×SC/IV interaction=0.085
Primary: raw GDR
P1–P99 winsorized GDR
P1–P99 trimmed raw GDR
Raw GDR, ≥3 slope points
Reference creatinine definition B
Reference creatinine definition C
0.90
0.95
1.00
1.05
Adjusted hazard ratio per 10-mg/dL/h higher GDR

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