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Insulin therapy associated relative hypoglycemia during critical illness

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ABSTRACT

Purpose: In critically ill diabetes patients, relative hypoglycemia (RH) (a decrease in glucose ≥30% below pre-admission levels, as estimated by HbA1c) is associated with greater mortality and absolute hypoglycemia. We investigated the epidemiology and outcomes of RH when it was associated with insulin therapy.
Methods: We performed retrospective analysis of a cohort of critically ill patients with diabetes who received insulin in the intensive care units (ICUs) of a tertiary hospital. The primary outcome was 28-day mortality with respect to insulin therapy associated relative hypoglycemia (ITARH).
Results: ITARH occurred in 184 (42%) of insulin-treated patients. ITARH was associated with a higher HbA1c (8.6% vs 6.6%, $p < 0.001$), a higher glycemic variability index (121 vs 75.1 $mmol^2/L^2/h$/week, $p < 0.001$) and more absolute hypoglycemia (18.5% vs 3.94%, $p < 0.001$). Its frequency peaked about 5 h after initiation of insulin therapy. ITARH was associated with a greater risk of subsequent hypoglycemia (adjusted HR 3.5, 95% CI 1.7–6.8) but not mortality (HR 1.2, 95% CI 0.7–2.2).
Conclusions: ITARH is common in insulin treated critically ill diabetes patients and associated with poorer glycemic control. Unlike reports of RH in general, it is not associated with mortality, suggesting that the prognostic implications of RH differ according to its context.

1. Introduction

Glucose levels are ideally closely monitored and controlled in intensive care unit (ICU) patients because both hypoglycemia and hyperglycemia are considered harmful [1]. However, the risk associated with hyperglycemia is complex and may be affected by the presence of chronic pre-admission hyperglycemia [2]. For example, diabetes patients have less evidence of benefit from stricter glycemic control targets compared with non-diabetes patients [3-6], and also less evidence of harm from hyperglycemia [7]. This difference may be due to being more prone and sensitive to the harmful effects of hypoglycemia or even relative hypoglycemia (RH). RH has been defined as a rapid decline of ≥30% in glucose levels below usual pre-admission levels (as estimated by HbA1c) despite not reaching absolute hypoglycemic levels (glucose <4 mmol/L) [8].

We recently described the epidemiologic features of RH in critically ill diabetes patients [8]. We found that RH was common, which was unsurprising given a 30% decline from average glucose is within target glycemic range for many ICUs. We found that RH was predictive of higher mortality and higher rates of subsequent hypoglycemia. Similarly, other studies have demonstrated a consistent signal that relative hypoglycemia (also described as a low glycemic gap) is associated with mortality [9-11].

Accordingly, we aimed to evaluate the interaction between insulin therapy and RH in diabetes patients admitted to ICU. We aimed to test the hypothesis that such ITARH would have a different association with hypoglycemia and mortality from that reported with RH in general.

2. Method

We studied diabetes patients admitted to the ICUs of a tertiary hospital. Adult patients only were included. Patients were excluded if there was missing data on timed blood glucose measurements, timed insulin administrations, HbA1c, coded diabetes diagnosis and data to calculate APACHE III score (Fig. 1).

Abbreviations: Intensive care unit, (ICU); Relative hypoglycemia, (RH); Insulin therapy associated relative hypoglycemia, (ITARH).

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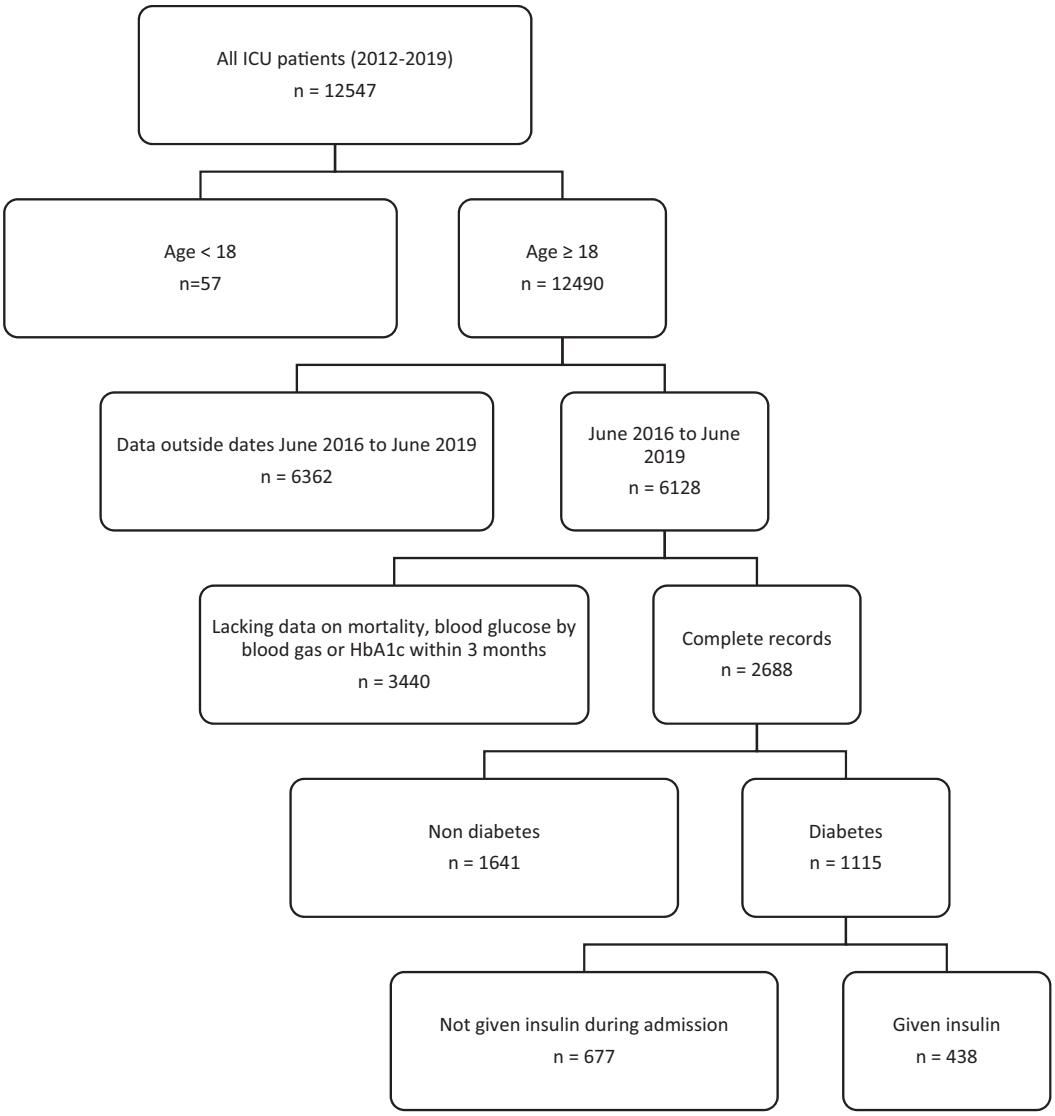

Fig. 1. Inclusion and exclusion criteria for study population.

The study was approved by the Institutional Human Research Ethics Committee, which waived the need for informed consent for the extraction and analysis of data from their Electronic Medical Record.

We obtained data on diabetes status according to prior coded diagnosis, glucose levels with timestamps for each measurement, HbA1c levels strictly within 3 months of admission and data on clinical outcomes. Patients were considered to have diabetes if they had a coded diagnosis of diabetes or their HbA1c was ≥6.5%. Insulin doses were recorded with timestamps and cumulative insulin doses per hour were calculated. The average pre-admission glucose was calculated according to Nathan's formula [12].

Data were available in electronic format from June 2016 to June 2019. Analysis was limited to regular insulin (Actrapid) therapy because its administration was the standard agent for insulin therapy in all ICU patients.

During the above period, the study ICUs targeted relatively liberal glucose control with a glucose target between 10 and 14 mmol/L in diabetes patients (type 1 and 2) as previously reported [13]. According to this protocol, insulin was ceased if glucose dropped below 6 mmol/L (Supplementary Fig. 1). Blood glucose levels were obtained exclusively from blood gas measurements to ensure the highest level of accuracy.

Insulin therapy associated relative hypoglycemia (ITARH) was defined as any episode of RH (a decrease to a glucose level ≥ 30% below the estimated pre-admission levels but above absolute hypoglycemic levels) in an insulin dependent patient (received insulin during ICU admission). Hypoglycemia was defined according to the standard definition glucose <4 mmol/L. The primary outcome was 28-day mortality with respect to ITARH and the secondary outcome was hypoglycemia after ITARH.

2.1. Statistical analysis

Summary statistics were generated for the insulin receiving study population and stratified according to presence of ITARH. The frequency of RH over time with respect to last insulin increase was also calculated.

Average glucose levels were estimated with time-weighted analysis. Normality was not assumed. Thus, all numerical data were compared with the Mann-Whitney *U* test. Categorical data were compared with the Chi-squared test. Kaplan Meier curves were plotted according to ITARH using standard statistical methods and compared using the log-rank test [14].

The occurrence of ITARH was graphed after various hypoglycemia inducing events: any insulin administration, insulin bolus,

commencement of insulin infusion or increase in insulin infusion. The frequency of ITARH within 4 h after insulin was counted both per patient and then per insulin administration.

The primary outcome of 28-day mortality was assessed according to the presence of ITARH using Cox regression models. The secondary outcome hypoglycemia was stipulated to occur after ITARH by treating ITARH as a binary and time dependent covariate. Univariable and multivariable Cox regression analyses were performed [8]. Covariates were included in the multivariable model if they carried a $p < 0.2$ in the univariable analysis. Covariates considered are listed in Supplementary Table 1. Collinearity was quantified with the Generalized Variance Inflation Factor [15]. Analysis was repeated in subgroups with HbA1c $< 8\%$ and HbA1c $\geq 8\%$.

The p level for significance was set at <0.05. Analysis was completed with R 3.6.1 [16].

3. Results

3.1. Study patients

We identified 438 diabetes patients who received insulin in ICU and fulfilled other inclusion and exclusion criteria. This was a mixed population of medical and surgical patients. They remained in ICU a median duration of 4 days and received a median dose of 75 units insulin over this time. A total of 10% experienced hypoglycemia, most of which was moderate hypoglycemia (2.3–4 mmol/L) and which occurred a median of 1.5 days after admission (Table 1).

Overall, 184 (42%) insulin-treated diabetes patients experienced ITARH. Those who experienced ITARH were more likely to be admitted from the Emergency Department and less likely to be surgical patients (both $p < 0.001$) (Table 1). They also had multiple markers of worse glycemic control with higher maximum glucose levels, higher glycemic lability index, higher HbA1c and were much more likely to experience hypoglycemia (all $p < 0.001$) (Table 1). In addition, they received a higher total dose of insulin therapy in ICU ($p = 0.025$) (Table 1). In patients with HbA1c ≥ 8% ITARH was much more common and occurred in 75% of patients ($n = 117$), compared to 24% ($n = 67$) of patients with HbA1c <8% (Supplementary Table 2). ITARH was not associated with a higher or lower APACHE III, although patients with ITARH were less likely to require intubation ($p = 0.026$) (Table 1).

Of the patients who experienced ITARH, 69% occurred within 240 min after insulin administration. In this group, 50.4% of patients recorded ITARH after a bolus, commencement of insulin infusion or increase in infusion; whereas the remaining 49.6% of patients experienced ITARH only during a stable insulin infusion or shortly after insulin was ceased (Table 2).

Out of 24,104 h of insulin administered, 1843 (7.6%) were followed within 4 h by ITARH with the majority of these (1666 h) occurring during stable or decreasing insulin infusion. By contrast, of 2491 increases in insulin infusion rate, only 111 (4.5%) were followed within 4 h by ITARH (Table 3).

The frequency of ITARH peaked around five hours after addition of insulin therapy, with the lowest rate just before or at the time of insulin administration. However, a higher frequency of glucose measurements

Table 1
Summary statistics comparing patients with diabetes who received insulin and who experienced ITARH to those who did not experience ITARH.

Variable	All patients	ITARH	No ITARH	*p*-value*
General features				
n	438	184	254	–
Age	65.6 (56.9–73.7)	64 (53.9–72)	66.8 (59–74)	0.021
Proportion male	285 (65.2%)	115 (62.8%)	170 (66.9%)	0.433
Proportion of surgical patients	227 (51.8%)	71 (38.6%)	156 (61.4%)	<0.001
Proportion from emergency department	92 (21.1%)	59 (32.2%)	33 (13%)	<0.001
Proportion from ward	110 (25.2%)	49 (26.8%)	61 (24.1%)	0.603
Proportion from operating room	228 (52.3%)	73 (39.9%)	155 (61.3%)	<0.001
Proportion from other ICU	6 (1.38%)	2 (1.09%)	4 (1.58%)	0.988
Severity of disease				
APACHE III score	54 (41–76)	59 (43–77.5)	53 (41–76)	0.377
Proportion hospital mortality	70 (16%)	30 (16.3%)	40 (15.7%)	0.98
Proportion ICU mortality	58 (13.2%)	26 (14.1%)	32 (12.6%)	0.746
Hospital stay (days)	14 (8.11–27)	14 (7.93–31.5)	14 (8.21–25.9)	0.916
ICU stay (hours)	92.5 (44–189)	97.2 (46.4–222)	83.2 (43.1–175)	0.047
Proportion cardiac arrest	16 (3.69%)	7 (3.85%)	9 (3.57%)	1
Proportion Intubated during admission	289 (66%)	110 (59.8%)	179 (70.5%)	0.026
Proportion non-invasive ventilation during admission	67 (15.3%)	27 (14.7%)	40 (15.7%)	0.862
Proportion requiring hemofiltration	71 (16.2%)	26 (14.1%)	45 (17.7%)	0.382
Glycemic control				
Previously diagnosed diabetes	407 (92.9%)	169 (91.8%)	238 (93.7%)	0.577
Maximum glucose (mmol/L)	18.2 (16–21.3)	20 (16.9–23.1)	17.4 (15.4–19.7)	<0.001
Minimum glucose (mmol/L)	7.15 (5.5–8.6)	5.6 (4.5–7)	8 (6.8–9)	<0.001
Mean glucose (mmol/L)	12.2 (11–13.3)	12.1 (10.6–13.3)	12.2 (11.3–13.3)	0.174
Standard deviation glucose	2.86 (2.18–3.65)	3.38 (2.73–4.47)	2.51 (1.95–3.11)	<0.001
Coefficient of variation glucose	23.8 (18.4–29.4)	28.4 (22.6–36.7)	20.9 (16.3–25.4)	<0.001
Glycemic lability index ($mmol^2/L^2/h/week$)	86.3 (53.2–152)	121 (70.3–206)	75.1 (45.4–115)	<0.001
HbA1c (%)	7.3 (6.3–8.6)	8.55 (7.5–10.4)	6.6 (5.9–7.4)	<0.001
Absolute hypoglycemia	44 (10%)	34 (18.5%)	10 (3.94%)	<0.001
Moderate hypoglycemia	41 (9.36%)	31 (16.8%)	10 (3.94%)	<0.001
Severe hypoglycemia	3 (0.685%)	3 (1.63%)	0 (0%)	0.146
Number of blood gases measured in ICU	26 (15–54)	28 (17.8–65.2)	25.5 (14–48.8)	0.016
ITARH	184 (42%)	184 (100%)	0 (0%)	<0.001
Time to hypoglycemia (days)	1.48 (0.285–7.1)	2.09 (0.339–5.89)	0.551 (0.165–11.5)	0.516
Time to RH (days)	0.589 (0.161–1.5)	0.589 (0.161–1.5)	–	–
Cumulative dose regular insulin during ICU admission (units)	75 (22–258)	89 (27–321)	65.5 (18.2–207)	0.025
Mean regular insulin dose or rate (units/h)	2.84 (2–4)	3.24 (2.2–4.22)	2.67 (2–3.85)	0.005
Mean glucose prior to insulin administration	9.25 (6–13.4)	10.3 (6–14.5)	8.71 (6–13)	0.023

Results are reported as median (IQR) or as n (%) and were calculated on a per-patient basis; *p-value is from the Mann-Whitney U test for numerical outcomes or chi-squared test for binary outcomes compares diabetes patients who experience ITARH with those who do not. Moderate hypoglycemia 2.3–3.9 mmol, severe hypoglycemia <2.3 mmol.

Table 2
Summary of insulin administration characteristics preceding an episode of relative hypoglycemia.

Phenomenon	Number of patients (percentage of all ITARH)
Any ITARH	184 (100%)
ITARH within 4 h of any insulin	127 (69%)
ITARH within 4 h of insulin bolus	5 (2.7%)
ITARH within 4 h of commencement of insulin infusion	43 (23%)
ITARH within 4 h of insulin infusion rate increase	38 (21%)
ITARH during stable/decreasing insulin infusion*	118 (64%)
ITARH within 4 h of insulin bolus, commencement of infusion or infusion rate increase	64 (35%)

* Please note that as many patients had multiple episodes of ITARH and variable insulin regimes, many patients experienced ITARH at one time during a stable insulin infusion and at another time after addition of insulin therapy. As calculation occurred on a per patient basis, the percentages add to over 100%. By contrast, 49.6% of patients experienced ITARH but never within 4 h of bolus, commencement of insulin infusion or increase in infusion rate. Moreover, please note that this 4 h window was used for the generation of this table but was not a requirement for the definition of ITARH in general.

was made shortly after addition of insulin therapy so the proportion of glucose events that were ITARH was also calculated (Fig. 2). ITARH occurred a median 14 h after ICU admission (Table 1). Amongst those who experienced ITARH, it occurred an average of 7 times during ICU admission. Although a 30% relative decline in glucose was required to define ITARH, the median level reached in each patient who experienced ITARH was a 45% decline (Supplementary Fig. 2).

3.2. Clinical outcomes according to the presence of ITARH

There was no difference in time to mortality censored at 28 days as displayed by Kaplan Meier survival plots (Supplementary Fig. 3). Similarly, both unadjusted (Supplementary Table 1) and adjusted (Fig. 3) Cox regression analysis demonstrated no significant association between ITARH and time to mortality within 28 days. There was no dose response in that a larger relative decrease in glucose did not correlate with a higher mortality (Supplementary Table 3). Similarly, in patients stratified by HbA1c <8% and HbA1c ≥ 8%, ITARH was not associated with mortality (adjusted HR 1.1 95% CI 0.6–2.0 and 1.3 95% CI 0.2–6.9 respectively) (Supplementary Fig. 4, Supplementary Fig. 5, Supplementary Table 4 and Supplementary Table 5). Generalized variance inflation factors did not show evidence of significant collinearity (Supplementary Table 6, Supplementary Table 7 and Supplementary Table 8).

The secondary outcome of hypoglycemia was higher after ITARH (adjusted HR 3.5 95% CI 1.7–6.8) (Fig. 4). Hypoglycemia was also strongly associated with the glycemic lability index, but adjustment for this or other variables did not significantly change the association between ITARH and hypoglycemia (Fig. 4 and Supplementary Table 9). There was also no evidence of significant collinearity (Supplementary Table 10). When hazard ratios for hypoglycemia after ITARH were stratified by HbA1c similar results were attained although confidence intervals were wide even for univariate calculations (for HbA1c < 8%: 3.6 95% CI 1.5–8.8 and for HbA1c ≥ 8%: 5.7 95% CI 1.3–25.1) (Supplementary Table 11 and Supplementary Table 12).

Table 3
Frequency of ITARH after insulin administration.

Type of insulin	Frequency ITARH within 4 h of insulin (%)	Mean hourly dose (units)
Any insulin administration	1843 (7.6%)	3.6
Insulin bolus	5 (6%)	4.7
Commencement of insulin infusion	61 (5.8%)	3.1
Insulin infusion rate increase	111 (4.5%)	5.6
Stable/decreasing insulin infusion*	1666 (8.1%)	3.4

Insulin administration counted on an hourly basis, not calculated per patient. Percentage refers to the proportion of insulin administrations followed within 4 h by ITARH.
* Insulin administration that was not a bolus, commencement of infusion or infusion rate increase.

4. Discussion

4.1. Key findings

We conducted a detailed study to examine the incidence, patient characteristics and outcome associations of insulin therapy associated relative hypoglycemia (ITARH). We found that ITARH was associated with other measures of poor glycemic control including high glycemic lability and high baseline glucose. Moreover, ITARH was common even when the insulin infusion had reached a stable rate. ITARH peaked 4–6 h after insulin administration, however the high rate of ITARH was partly an artefact of more regular glucose measurements at this time. Importantly, while ITARH was strongly associated with subsequent hypoglycemia, there was no significant association between ITARH and mortality. These findings were mirrored in subgroups stratified by HbA1c, although this study was underpowered to demonstrate a significant difference between these subgroups.

4.2. Biological plausibility

The notion that ITARH is clinically significant is biologically plausible, as relative decreases in glucose are logical harbingers of even deeper subsequent falls in concentration which may adversely affect outcome. Hypoglycemia increases inflammatory molecules known to have pro-atherogenic and pro-thrombotic effects, especially in diabetes patients [17]. Moreover, large relative decreases in glucose that remain in the normoglycemic range may induce autonomic symptoms, epinephrine elevation and cortisol elevation, in patients with poorly controlled diabetes, which has been hypothesized to be a source of cardiovascular stress [18-23].

In critically ill diabetes patients, RH is heterogeneous in etiology. In particular, some episodes of RH may be spontaneous and induced by the severity of the underlying disease via mechanisms such as diminished gluconeogenesis, adrenal insufficiency and liver failure. By contrast, there may be an iatrogenic component to hypoglycemia contributed to by fasting or various drugs, but most notably insulin therapy [24]. Finfer demonstrated that insulin treatment therapy modulated the association between hypoglycemia and mortality [25]. Similarly, it is possible that insulin therapy associated RH (ITARH) has specific implications and associations which differ from disease-associated RH. Knowledge of such implications and associations can help inform clinician perceptions and management.

4.3. Relationship to previous studies

This is the first observational study to analyse the epidemiology of ITARH. It is generally accepted that hypoglycemia is associated with worse outcomes including hospital mortality [1,26]. However, the extent to which pre-morbid glycemic control affects tolerance to hypoglycemia or hyperglycemia is controversial. Several studies have demonstrated lack of association between hyperglycemia and mortality in diabetes patients [27,28]. Similarly, diabetes patients appear to tolerate higher glucose variability [29], while being at higher risk of hypoglycemia [3]. In this context, the fact that RH in diabetes patients has been associated with increased risk of both subsequent hypoglycemia and mortality [8] invites the investigation of less strict protocols for glycemic control and the design of studies comparing liberal to conventional glycemic control in diabetes ICU patients. Therefore, understanding whether RH occurring in association with insulin therapy carries the same risks of RH in general is important.

Several trials have investigated altering glycemic control for diabetes patients, often adopting more liberal glycemic control [13,30-34].

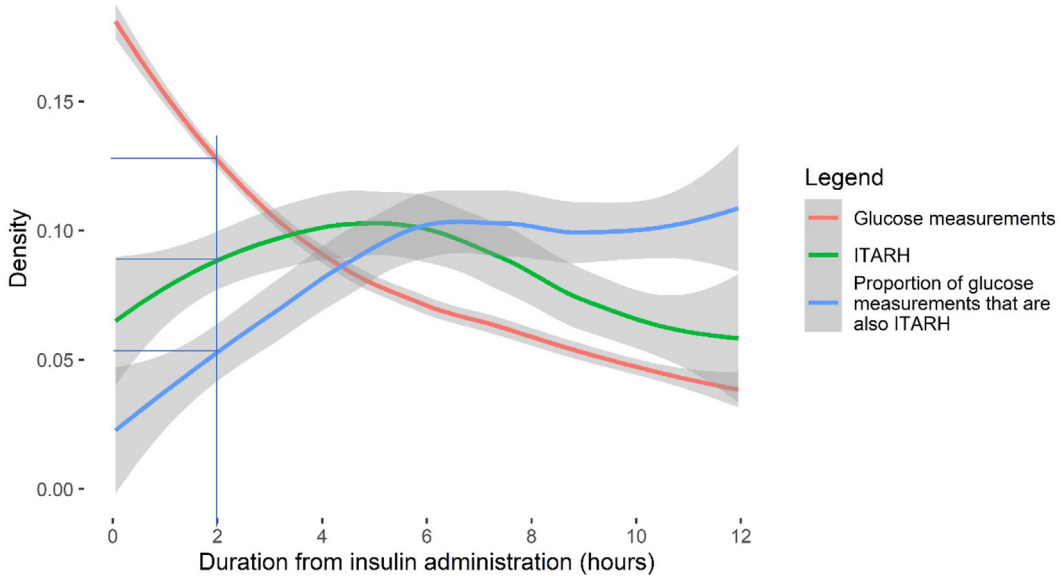

Fig. 2. Density plot comparing number of ITARH events to number of glucose measurements measured over time from addition of insulin therapy.
Addition of insulin therapy defined as an insulin bolus, starting an infusion or increasing the rate of infusion. It did not include continuing an infusion without increasing the rate. Curves generated by locally estimated scatterplot smoothing (LOESS) on a normalised histogram with bin width 0.1 h. Counted per insulin (not a per patient basis). Density refers to the proportion of patients who experienced events (either measurement of glucose or ITARH) after addition of insulin therapy.

However, even the largest such trial was probably underpowered to detect a mortality benefit as in this trial both diabetes and non-diabetes patients experienced individualized glycemic control that resulted in largely similar mean glucose and glycaemia standard deviation [33]. It is currently unclear how to best individualize glycemic control in critically ill diabetes patients and a better understanding of the clinical significance of measures of glycemic variability such as relative hypoglycemia will be required.

4.4. Implication of study findings

Our findings imply that, in diabetes patients, ITARH is a marker of poor and more difficult to achieve pre-admission and post admission glycemic control. Moreover, they imply that ITARH episodes are commonly observed within six hours of starting or changing insulin infusion and that half occur after a bolus, commencement or increase in insulin infusion. Finally, our findings demonstrate a strong relationship between ITARH and subsequent hypoglycemia but not with mortality, implying that the previously reported association between RH and mortality is more likely to reflect illness severity than insulin therapy induced harm.

4.5. Strengths and weaknesses

This study has several strengths. Firstly, timestamped insulin infusion and glucose levels allowed specific investigation of insulin therapy associated RH. Second, this is the first study to investigate glycemic variability after insulin in hospitalized patients. Consequently, novel findings about the iatrogenic effects of insulin could be uncovered. The vastly predominant form of insulin administration was by continuous

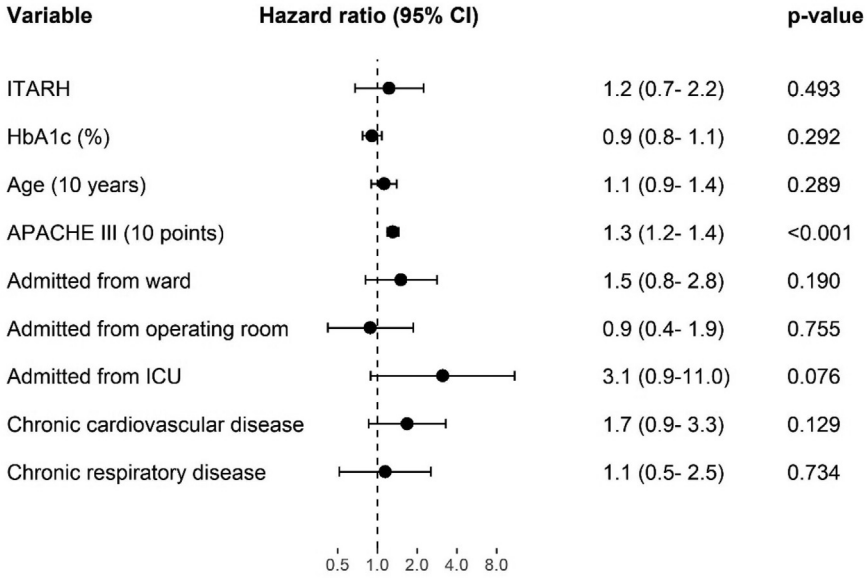

Fig. 3. Hazard ratio of 28-day mortality with multivariable adjustment by Cox regression analysis.

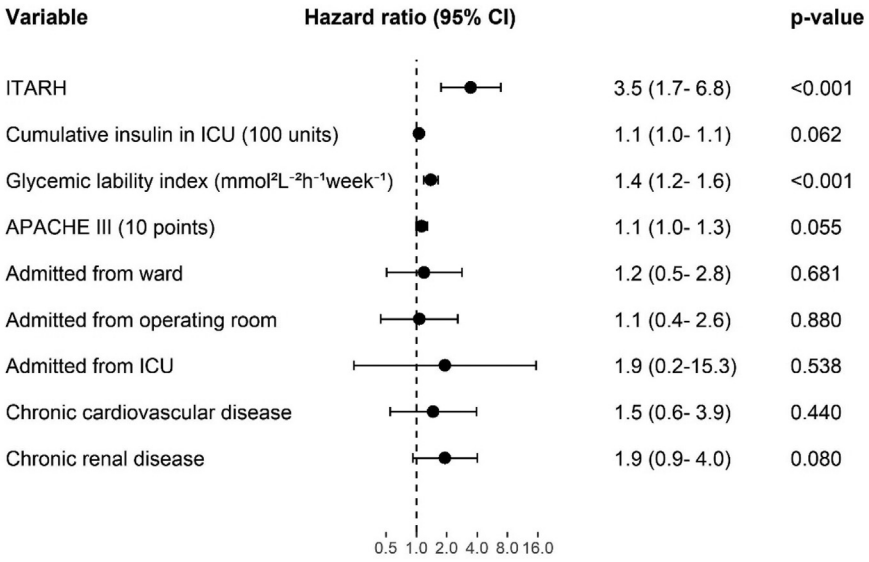

Fig. 4. Hazard ratio of absolute hypoglycemia with multivariable adjustment by Cox regression analysis.

IV insulin infusion, thus minimizing the use of bolus administration and the presence of sudden changes in insulin dose. All glucose levels used were measured with blood gas sampling, minimizing measurement error. The observation that ITARH is a major risk factor for subsequent hypoglycemia and that half of RH episodes occurred without increasing insulin therapy has clinical implications.

We acknowledge several limitations. First, this was a single centre study of ICUs within a university affiliated hospital which practices more liberal glycemic control than some other centres [13]. However, these ICUs accept a mix of medical and surgical patients and are broadly representative of practices elsewhere in Australia, which have trended away from strict glycemic control in diabetes patients.

Secondly, confidence intervals were wide and the study may have been underpowered to detect a true but weak relationship between ITARH and mortality. This limitation is especially true for subgroup analysis stratifying results by HbA1c and these results should be interpreted with caution. This single centre study did not have additional data on metrics such as BMI at baseline and nutritional intake nor the power to analyse these. It would be informative in future studies to pursue further subgroup analysis according to baseline diagnoses and RH severity.

Thirdly selection bias was introduced by missing data, as over half of patients were excluded due to missing records. Missing data were mostly (72%) due to lacking HbA1c or glucose measurements, however, as data were collected electronically, these data were also not available to clinicians. Hence the patients excluded from the study (mostly those without a HbA1c measured in hospital or who did not have a blood gas taken to measure glucose) were likely less relevant to the present study.

Furthermore, selection bias was introduced by Cox regression analysis, which intrinsically over-represents longer stayers. Reassuringly, univariate Cox regression (which had smaller confidence intervals) as well as the chi squared test (which had better power and did not bias for long-stayers) demonstrated similar results to the multivariate Cox regression analysis.

Fourthly, these findings were from observational data and confounding was inevitable. For example, the study ICUs may have been more likely to admit patients with high insulin requirements. There are theoretical concerns that markers of glycemic variability may be collinear with ITARH. Reassuringly, generalized variance inflation factors were not suggestive of collinearity and results were similar irrespective of multivariable adjustment. As with most observational data, these results were also subject to surveillance bias. Almost seven blood gas measurements were performed on average per day; however this approach will have inevitably missed RH between measurements.

Lastly, ITARH is a new concept and lacks a well-validated definition and several alternatives may be proposed. Our definition did not address the detection of non-insulin associated RH because patients who received insulin, by definition, could only experience ITARH instead or RH. Furthermore, ITARH does not specify iatrogenic RH; false positives would include small or temporally distant insulin doses that did not in fact cause RH and false negatives would include non-insulin causes of hypoglycemia such as fasting or oral hypoglycemic medications. Indeed, 31% of patients who experienced ITARH did not have this event occur within 240 min of insulin administration. Nevertheless, since insulin is the main way glucose is controlled in ICU and most episodes of ITARH were temporally related to insulin, the definition is simple and biologically plausible. Further studies will be required to expand on measures of glycemic control especially in patients not receiving insulin.

5. Conclusions

In critically ill diabetes patients, ITARH affects almost half of those receiving insulin infusion. It occurs most commonly amongst patients with other markers of poorly controlled diabetes and can occur during both increases in insulin infusion rates or during steady insulin infusion. Like reports of RH in general, ITARH was associated with a greater than three-fold increase in the risk of subsequent absolute hypoglycemia. Unlike reports of RH in general, however, ITARH was not significantly associated with mortality. This suggests that greater vigilance and cautious adjustments of insulin infusion rates in ITARH patients are logical to minimize the risk of absolute hypoglycemia. However, it also suggests that RH may be less biologically and clinically significant in ICU patients with diabetes who are receiving insulin than reported for RH in general and that the prognostic implications of RH differ according to its context.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2022.154018.

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