

Assessing the Predictive Performance of the STAR Glycemic Control Framework on the MIMIC-III Adult ICU Cohort

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Abstract: Glycemic control in intensive care unit (ICU) patients remains difficult due to inter- and intra-patient variability and the risk of hypoglycemia associated with intensive insulin therapy. The STAR model-based glycemic control framework has demonstrated safe, effective performance in clinical use, thanks to patient-specific physiological modeling and stochastic prediction of future blood glucose (BG) levels. This study provides the first external validation of STAR’s predictive performance using the MIMIC-III database to assess its generalizability to a large, heterogeneous ICU cohort.

ICU patients receiving intravenous insulin were identified, and 9-hour data blocks were created consisting of 6 hours of past input data (BG, insulin and nutrition) and 3 hours of forward input data without BG levels. After quality filtering, 184,295 blocks from 2,711 ICU stays were analyzed. STAR was evaluated as a black-box model, comparing its predicted 3-hour BG ranges with real clinical BG measurements. Accuracy was defined as the proportion of measurements falling within the predicted range, and mispredictions were further assessed by direction, severity, BG levels, and diabetes.

Overall accuracy was 75%, with only 2% of values falling below 4.4 mmol/L and 0.04% below 2.2 mmol/L, which are very similar to those of STAR in clinical use. Accuracy remained above 70% across BG levels at prediction time, except below 4.4 mmol/L, where accuracy decreased to 58%. Stratified analysis showed accuracy >75% for patients without diabetes or with type 2 diabetes, and 65% for those with type 1 diabetes. Although approximately 10% of values were below the predicted range, these rarely posed clinical concern and are likely related to conservative modeling.

These results demonstrate that STAR maintains strong predictive performance on an external dataset and can safely anticipate BG evolution up to 3 hours in advance. The predicted results match those of STAR in clinical use, providing further confidence in model’s validity. Overall, these results support the broader use of STAR across clinical environments and within computerized decision-support systems to enhance the safety and efficacy of glycemic control in adult ICU patients.

Keywords: glycemic control, hypoglycemia, hyperglycemia, insulin, critical care, digital twin

1. INTRODUCTION

Glycemic control in intensive care unit (ICU) patients remains challenging due to substantial inter- and intra-patient variability (Chase et al., 2018, Egi et al., 2009, Finfer et al., 2009, Preiser et al., 2009, Suhaimi et al., 2010, Uyttendaele et al., 2019). The associated risk of hypoglycemia often outweighs potential benefits of maintaining normoglycemia (Bagshaw et al., 2009, Egi et al., 2010, Uyttendaele et al., 2019). Consequently, most clinical guidelines recommend permissive hyperglycemia rather than tight glycemic control, even though normoglycemic levels are associated with improved patient outcomes (Chase et al., 2010, Egi et al., 2009, Krinsley et al., 2015, Penning et al., 2014, Signal et al., 2012).

Recent studies, however, have shown that safe glycemic control can be achieved using patient-specific computerized protocols explicitly accounting for individual patient-specific variability (Stewart et al., 2016, Uyttendaele, 2023). These systems rely on model-based approaches to identify and predict patient-specific responses to insulin over time using routinely collected clinical data (Evans et al., 2012, Lin et al., 2008, Lin et al., 2011). As a result, hypoglycemia can be minimized while blood glucose (BG) levels are maintained within the normoglycemic range.

This study assesses the predictive performance of the clinically validated STAR glycemic-control framework using independent patient data from the MIMIC-III database (Arévalos, 2021, Robles Arevalo et al., 2021). The goal is to assess its generalizability to a different critically ill patient

cohort, treated under a different clinical practice culture. The analysis provides an external validation of the STAR model's predictive accuracy, fairness, and robustness on a dataset which was never used for its development and highlights potential caveats or limitations.

2. METHODS

2.1 STAR Framework

STAR is a clinically validated, model-based glycemic-control framework that has been extensively used and constitutes the standard of care in Christchurch Hospital, New Zealand (Stewart et al., 2016, Uyttendaele, 2023). It combines physiological modelling with a stochastic approach to guide insulin and nutrition dosing in adult ICU patients (Evans et al., 2012, Lin et al., 2008).

Clinical data, including BG measurements, insulin and nutrition administration, and diabetes status, are used to identify patient-specific insulin sensitivity (characterizing the effect of insulin on insulin-mediated glucose uptake) over time (Lin et al., 2011). A stochastic model predicts possible future changes in insulin sensitivity (90% confidence interval) based on each patient's unique profile and recent trends, enabling simulation of BG evolution for the next 3 hours under different treatment options (Lin et al., 2008).

STAR then evaluates all feasible treatments and recommends optimal options based on safety constraints and target BG ranges (Evans et al., 2012). Nurses can accept or adapt these recommendations according to clinical judgment.

STAR is implemented as a point-of-care web application (Glucoméo by Insilicare, Belgium) connected to the electronic health record, improving workflow, providing alarms and reminders, and reducing human error. The validation presented in this study was therefore performed using the Glucoméo software implementation of STAR.

2.2 Analysis

In this study, STAR is treated as a black-box model providing a predicted BG range for the next 1–3 hours, with a claimed accuracy of 75%, based on the most recent 6 hours of clinical data. Importantly, no treatment recommendations are generated in this analysis. Retrospective data, including the treatment delivered, is used solely to evaluate predictive performance. Thus, this study examines prediction accuracy only, not the clinical performance or safety of STAR-guided glycemic control.

Adult ICU patients (>18y/o) who received intravenous (IV) insulin were extracted from the MIMIC-III database following criteria established in a previous study (Arévalos, 2021, Robles Arevalo et al., 2021). For each patient, 9-hour data blocks were created: 6 hours of input data (BG, insulin, nutrition) prior to the prediction time, and 3 hours of post-prediction data (insulin and nutrition only).

Additional preprocessing ensured model compatibility. Blocks with no insulin or nutrition were removed. Blocks containing subcutaneous insulin, or those lacking at least three BG measurements within the first 6 hours, were also excluded to

ensure data density. Furthermore, each real BG value used for validation had to occur at least 30 minutes after the prediction time to avoid unphysiological fluctuations or simultaneous arterial/venous BG assays.

For each block, the model-predicted BG range was compared with the actual clinical BG value measured during the 3-hour prediction window. Accuracy was defined as the proportion of real BG values falling within the predicted range (Figure 1).

Mispredictions were classified as above or below the predicted range. Clinically, values below the range are of particular concern due to the risk of hypoglycemia, especially severe hypoglycemia ($BG < 2.2$ mmol/L or 40 mg/dL). Accordingly, misprediction falling below 4.4 mmol/L (the lower threshold of normoglycemia) and below 2.2 mmol/L were specifically reported. In addition, the mean absolute error (MAE) was calculated for all below-range mispredictions to better quantify their severity and assess their potential impact on safety and model robustness.

Prediction performance was also analyzed relative to the BG level at prediction time, as this affects clinical risk. For example, STAR's physiological model is typically more accurate at normoglycemic levels and less accurate at very high BG (>10 mmol/L) due to pronounced insulin resistance, prompting more conservative (safety-biased) predictions (Lin et al., 2011). In addition, a misprediction into severe hypoglycemia is more likely if the BG is already lower. Results were also compared by diabetes status to investigate the influence of comorbid diabetes on model performance.



Figure 1. Six hours of clinical data are used to generate a predicted blood glucose (BG) range (dotted) for the subsequent 3-hour period following the prediction time (“now”). In this example, the observed BG value lies within the predicted range.

3. RESULTS

3.1 Patient Cohort

From the original 12,210 ICU admission stays (9,518 patients) available in the MIMIC-III database (Arévalos, 2021, Robles Arevalo et al., 2021), 4,296 admissions (3,996 patients) included IV insulin therapy. After preprocessing, 2,711 admissions (2,625 patients) met data-quality and density criteria for model input. In total, 184,295 9-hour blocks were generated for validation (Figure 2).

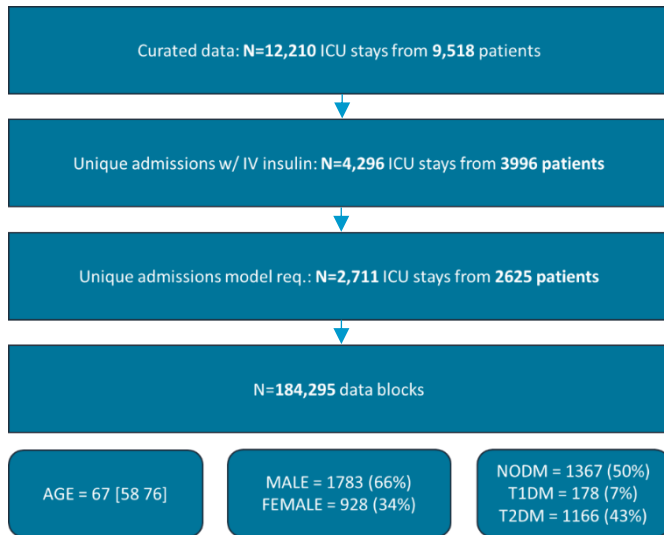


Figure 2. Processing of the MIMIC-III cohort. From 12,210 ICU admission periods, 2,711 satisfied the model input requirements for data quality and measurement density, resulting in 184,295 9-hour data blocks. The age and sex distributions are consistent with typical adult ICU populations. NODM = No diabetes mellitus, T1DM= Type 1 diabetes mellitus, T2DM = Type 2 diabetes mellitus.

The demographic characteristics of the 2,625 patients (median [IQR] age, sex distribution, and prevalence of type 1 diabetes mellitus (T1DM) were consistent with typical adult ICU populations. The prevalence of type 2 diabetes mellitus (T2DM) appeared higher than the ~25% typically reported in ICU cohorts; however, the results are expressed per ICU stays rather than per individual patient, which aligns with proportions reported in other studies and explains the apparent discrepancy.

3.2 Prediction Results

Results are summarized in Tables 1-2. The overall accuracy was 75% (Wilson score 95% CI: 74.8–75.2%), with 138,153 correct predictions out of 184,295. A total of 28,676 (16%) BG values were above the predicted range, and 17,466 (9%) were below. Of the latter, 3,970 (2%) were below 4.4 mmol/L, and 68 (0.04%) were in severe hypoglycemia (<2.2 mmol/L).

Accuracy remained above 70% across BG levels at prediction time (Table 1), except for BG < 4.4 mmol/L. In this range, accuracy dropped to 58% and the proportion of mispredictions below 4.4 mmol/L and 2.2 mmol/L increased to 4% and 0.2%, respectively.

The overall MAE was 0.86 mmol/L, and consistent across all BG levels at prediction time, except for BG > 10.0mmol/L. In this range, the 1.59 mmol/L MAE was significantly higher.

When stratified by diabetes status, accuracy exceeded 75% for patients with T2DM or without known diabetes, but was 65% for patients with T1DM. In T1DM, both above-range (22%) and below-range (14%) mispredictions were higher than in the full cohort (16% and 9%, respectively). In that group, the 0.2% of misprediction below 2.2 mmol/L was the highest.

4. DISCUSSION

Overall, the STAR black-box model successfully predicts BG evolution over a 3-hour period with an accuracy consistent with the claimed 75%, and robust over all BG level ranges at prediction time, except for BG<4.4 mmol/L (65%). In that case, 86% of mispredictions were above predicted range, not leading to critical safety concerns for the patients. In contrast, only 14% of the misprediction were below the range, from which 0.005% lead to severe hypoglycemia.

The low rates of mispredictions into hypoglycemic ranges (2% below 4.0 mmol/L; 0.04% below 2.2 mmol/L) indicate strong inherent safety. Among the 17,466 total below-range mispredictions, 23% fell below 4.4 mmol/L and 0.004% below 2.2 mmol/L, meaning that 77% posed no safety concerns. Moreover, in the STAR framework, predictions are simulated across multiple treatment options to ensure the lower bound exceeds 4.4 mmol/L (Evans et al., 2012). Consequently, the already low incidence of potentially harmful mispredictions would be further mitigated, consistent with the near-zero hypoglycemia rates reported in recently published clinical studies (Uyttendaele, 2023).

Of the 25% mispredictions, the 16% that fall above the predicted range can be explained by two factors. First, as described in the Methods, the physiological model used in STAR is known to perform best within the normoglycemic range. This is reflected in the results, where above-range mispredictions increase substantially when BG < 4.4 mmol/L (36%) and when BG > 10.0 mmol/L (Table 1). In the former case, STAR tends to be conservative, predicting lower ranges than clinically observed, which would translate into safer insulin dosing recommendations the STAR framework. In the latter case, BG levels are so high as to be physiologically atypical; under these conditions, the model saturates and assumes the possibility of sudden increases in insulin sensitivity, thereby avoiding predictions that could lead to excessive insulin dosing, a deliberate safety feature.

Regarding the remaining 9% of below-range mispredictions, these cases suggest that actual clinical BG levels were lower than anticipated due to higher-than-predicted insulin sensitivity. Notably, only about ~2% of all mispredictions fall into ranges that may raise safety concerns (<4.4 mmol/L). The MAE across BG levels further demonstrates that model error is smallest within the normoglycemic range. Importantly, typical ICU BG measurement error for bedside devices is reported to be approximately 15–20% (Freckmann et al., 2010, Garingarao et al., 2014, Uyttendaele et al., 2017). Therefore, the observed MAE of 0.86 mmol/L lies well within expected measurement variability, indicating that some mispredictions may reflect intrinsic BG measurement error rather than model inaccuracy.

It is also important to note that these misprediction rates may be conservative. In some cases, patients received little or no IV insulin or nutrition during the prediction window, reducing model accuracy because predictions depend more heavily on endogenous insulin secretion and glucose production model parameters. Although blocks completely lacking insulin or nutritional inputs were excluded, treatment administered after

the prediction time was not specifically assessed. Additional analyses removing such blocks may help clarify this phenomenon and potentially increase apparent accuracy.

When examining diabetes subgroups, accuracy remained above 75% in patients without diabetes or with T2DM (Table 2). Accuracy was lower (65%) in T1DM, but still encouraging given the known variability and treatment complexity of this population (Sechterberger et al., 2017). Importantly, the incidence of mispredictions that could lead to hypoglycemia remained extremely low across all subgroups, indicating consistent safety and fairness irrespective of diabetes status.

One limitation concerns the data and its interpretation. Although the dataset is comprehensive, several assumptions were required, and it was not always possible to ensure that all sources of carbohydrates and insulin were fully captured. Some manual effort was necessary to recover nutritional information, such as carbohydrate concentrations based on nutrition brand names. The authors made every effort to match this information accurately and believe that the curated dataset on which this work is based (Arévalos, 2021, Robles Arevalo et al., 2021) was already of high quality, thereby limiting potential sources of error.

The validation results obtained on this external cohort, used for the first time to evaluate STAR's performance and safety, are highly encouraging. The overall prediction accuracy of 75% for forecasting blood glucose evolution 3 hours in advance suggests that STAR can be integrated into a fully computerized protocol for guiding glycemic control in adult ICU patients. In particular, the model can be used to simulate BG trajectories under different insulin and nutrition dosages and to recommend appropriate treatments to nursing staff. When combined with additional safety constraints, STAR has the potential to significantly improve BG stability and overall control performance. Importantly, the model can predict and prevent severe hypoglycemia up to 3 hours before it occurs, thereby reducing complications, shortening ICU length of stay, and lowering overall healthcare costs. Safe and effective glycemic control is associated with improved ICU outcomes (Chase et al., 2010, Egi et al., 2009, Egi et al., 2010, Krinsley et al., 2006, Krinsley et al., 2011, Krinsley et al., 2015, Penning et al., 2014, Reed et al., 2007, Signal et al., 2012, Van den Berghe et al., 2001); thus, the hypoglycemia risk commonly linked with intensive insulin therapy can be minimized, potentially yielding substantial improvements in patient outcomes and mortality.

Table 1. Prediction accuracy defined as the proportion of measurements falling within the predicted range, and mispredictions were further assessed by direction (above/below), severity (mis-prediction below 4.0 mmol/L and 2.2 mmol/L), and BG level at prediction time. Data given as # (% of total). MAE = Mean Absolute Error (mmol/L).

	Overall	BG<4.4mmol/L	4.4≤BG≤8.0mmol/L	8.0<BG≤10.0mmol/L	BG>10.0mmol/L
Total	184,295 (100%)	7,113 (4%)	120,008 (65%)	33,112 (18%)	24,062 (13%)
Inside	138,153 (75%)	4,152 (58%)	90,695 (76%)	26,142 (79%)	17,164 (71%)
Above	28,676 (16%)	2,539 (36%)	18,554 (15%)	2,995 (9%)	4,588 (19%)
Below	17,466 (9%)	422 (6%)	10,759 (9%)	3,975 (12%)	2,310 (10%)
< 4.4 mmol/L	3,970 (2%)	284 (4%)	3,007 (3%)	468 (1%)	211 (0.9%)
< 2.2 mmol/L	68 (0.04%)	14 (0.2%)	27 (0.02%)	9 (0.03%)	18 (0.07%)
MAE mmol/L	0.86	0.93	0.69	0.87	1.59

Table 2. Prediction accuracy defined as the proportion of measurements falling within the predicted range, and mispredictions were further assessed by direction (above/below), severity (mis-prediction below 4.0 mmol/L and 2.2 mmol/L), and diabetes status. Data given as # (% of total). MAE = Mean Absolute Error (mmol/L).

	Overall	No Diabetes	T1DM	T2DM
Total	184,295 (100%)	64,300 (35%)	18,364 (10%)	101,631 (55%)
Inside	138,153 (75%)	49,792 (77%)	11,896 (65%)	76,465 (75%)
Above	28,676 (16%)	8,583 (13%)	3,979 (22%)	16,114 (16%)
Below	17,466 (9%)	5,925 (9%)	2,489 (14%)	9,052 (9%)
< 4.4 mmol/L	3,970 (2%)	1,302 (2%)	592 (3%)	2,076 (2%)
< 2.2 mmol/L	68 (0.04%)	15 (0.02%)	32 (0.2%)	21 (0.02%)

5. CONCLUSIONS

This study provides the first external validation of the STAR model-based glycemic control framework using the MIMIC-III database, demonstrating that STAR retains strong, fair, and robust predictive performance on a large and clinically diverse cohort that was not used in its development. The model achieved an overall 75% accuracy in forecasting blood glucose evolution over a 3-hour period, with very low rates of mispredictions leading to hypoglycemia. These results underscore the generalizability of STAR's physiological and stochastic modeling approach, even in the presence of substantial inter- and intra-patient variability and heterogeneous clinical practices.

Despite limitations inherent to retrospective data, including uncertainties in nutrition documentation and assumptions needed to reconstruct carbohydrate content, the findings indicate that STAR can reliably support computerized glycemic control workflows in adult ICU patients. The ability to simulate multiple treatment options and anticipate hypoglycemic risk hours in advance positions STAR as a valuable decision-support tool capable of improving safety, stabilizing glycemic outcomes, and reducing clinical workload.

Overall, this external validation provides strong evidence that STAR can be deployed more broadly to enhance ICU glycemic management, potentially improving patient outcomes while mitigating the risks traditionally associated with intensive insulin therapy.

ACKNOWLEDGEMENTS

This work was supported by the EU Horizon Europe R&I programme [agreement #101095435 – REALM]; the Service Public Fédéral Stratégie et Appui (BOSA) [Project DIGITWIN4PH]; and the EU H2020 R&I programme (MSCA-RISE-2019 call) [agreement #872488 – DCPM].

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