Received: 19 March 2020 | Revised: 4 May 2020 | Accepted: 10 May 2020

DOI: 10.1002/dmrr.3347

RESEARCH ARTICLE

WILEY

A performance score of the quality of inpatient diabetes care is a marker of clinical outcomes and suggests a cause-effect relationship between hypoglycaemia and the risk of in-hospital mortality

Alessandra Dei Cas[1,2] | Raffaella Aldigeri[1] | Valentina Ridolfi[1,2] | Angela Vazzana[2] | Anna Vittoria Ciardullo[3] | Valeria Manicardi[4] | Alessandra Sforza[5] | Franco Tomasi[6†] | Donatella Zavaroni[7] | Ivana Zavaroni[1,2] | Riccardo C. Bonadonna[1,2]

[1]Department of Medicine and Surgery, Università di Parma, Parma, Italy

[2]Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

[3]Azienda USL, Modena, Italy

[4]Azienda USL, Reggio Emilia, Italy

[5]Azienda USL, Bologna, Italy

[6]Azienda USL, Ferrara, Italy

[7]Azienda USL, Piacenza, Italy

Correspondence
Alessandra Dei Cas, Division of Endocrinology and Metabolic Diseases, Department of Medicine and Surgery, University of Parma and Azienda Ospedaliero-Universitaria of Parma, Via Gramsci 14, 43126 Parma, Italy.
Email: alessandra.deicas@unipr.it

Funding information
Programma di Ricerca RER/-Università 2010-2012-Area 2 Ricerca per il Governo Clinico

Abstract

Aims: To build a tool to assess the management of inpatients with diabetes mellitus and to investigate its relationship, if any, with clinical outcomes.

Materials and methods: A total of 678 patients from different settings, Internal Medicine (IMU, n = 255), General Surgery (GSU, n = 230) and Intensive Care (ICU, n = 193) Units, were enrolled. A work-flow of clinical care of diabetes was created according to guidelines. The workflow was divided into five different domains: (a) initial assessment; (b) glucose monitoring; (c) medical therapy; (d) consultancies; (e) discharge. Each domain was assessed by a performance score (PS), computed as the sum of the scores achieved in a set of indicators of clinical appropriateness, management and patient empowerment. Appropriate glucose goals were included as intermediate phenotypes. Clinical outcomes included: hypoglycaemia, survival rate and clinical conditions at discharge.

Results: The total PS and those of initial assessment and glucose monitoring were significantly lower in GSU with respect to IMU and ICU ($P < .0001$). The glucose monitoring PS was associated with lower risk of hypoglycaemia (OR = 0.55; $P < .0001$), whereas both the PSs of glucose monitoring and medical therapy resulted associated with higher in-hospital survival only in the IMU ward (OR = 6.67 $P = .001$ and OR = 2.38 $P = .03$, respectively). Instrumental variable analysis with the aid of PS of glucose monitoring showed that hypoglycaemia may play a causal role in in-hospital mortality ($P = .04$).

Conclusions: The quality of in-hospital care of diabetes may affect patient outcomes, including glucose control and the risk of hypoglycaemia, and through the latter it may influence the risk of in-hospital mortality.

KEYWORDS

clinical outcomes, diabetes, governance, hypoglycaemia, in-hospital, performance score

[†]Deceased

1 | INTRODUCTION

Diabetes mellitus (DM) is a global epidemic. Approximately 415 million adults worldwide[1] have DM and these estimates and the disease-related costs are expected to at least double in the next 25 years. Notably, 12% to 25% of patients admitted in medical wards, surgery and intensive care units have DM.[2] Hospitalized patients with DM show increased rate of complications—mostly infections, a more severe prognosis, an extended length of stay and doubled costs of care compared with hospitalized patients without DM.[3] In-hospital hyperglycaemia is closely related to adverse outcomes[4] and to short-term mortality in all clinical settings in patients with and without history of DM.[2,5,6] Accordingly, fair, but perhaps not tight, glucose control positively affects in-hospital morbidity, mortality and health care economic outcomes.[2,5,7] However, in-hospital achievement of appropriate glucose goals is hampered by several factors such as the severity of the intercurrent illness, medications and nutritional management. In addition, tackling glucose goals with intensive insulin regimens raises substantial concerns about the risks of (severe) hypoglycemic events with potential related adverse (cardiovascular) outcomes.[8-10] In-hospital management of diabetes in non-specialistic settings is indeed complex and the management of DM and hyperglycaemia still remains suboptimal with large differences between and within hospitals and clinical settings.[11]

Improving the current less than satisfactory in-hospital care of diabetes mellitus requires, among other things, to develop: (a) a tool to assess and (b) a training program for health professionals to raise the quality of inpatient diabetes care.

To date, no specific training programs for both physicians and nurses have been validated to raise the standards of diabetes care, and in-hospital diabetes management remains largely dependent on unstandardized individual/ward clinicians' awareness and specific competence.

The Governance of Hospitalized Diabetic patient in non-specialistic settings (GOVEPAZ) study is a cluster-randomized, active-control, two-parallel group, intervention study (clinicaltrials.gov identifier NCT02640768) conducted in a number of non-specialistic inpatient wards. GOVEPAZ was structured as a 2-stage study. In stage 1 (assessment), the aim of GOVEPAZ was to develop a performance score of the quality of inpatient diabetes care and to assess its cross-sectional validity as a marker of metabolic and clinical outcomes. In stage 2 (intervention), the aim of GOVEPAZ was to develop and to implement a structured educational program for health professionals to be compared with no educational intervention as to the efficacy in improving the performance score of inpatients diabetes care and some clinical outcomes. We herein present the results of stage 1 of GOVEPAZ.

2 | MATERIALS AND METHODS

2.1 | Study population

The study included non-selected individuals with diabetes prospectively and consecutively admitted within a 3-month period in three different non-specialistic wards from January 1, 2012, to May 14, 2014: Internal Medicine (IMU), Surgery (GSU) and Intensive Care (ICU) Units of six hospitals of the Emilia Romagna Region in Northern Italy (Parma, Piacenza, Montecchio Emilia, Ferrara, Carpi, Bologna). The main inclusion criteria were age ≥18 years and diabetes defined as fasting blood glucose ≥126 mg/dL (7 mmol/mol) or random blood glucose ≥200 mg/dL (11.1 mmol/mol) and/or HbA1c ≥6.5% (48 mmol/mol) and/or previous known diabetes or diabetes medication (according to American Diabetes Association criteria[12]) at admission. Main exclusion criteria were age ≤18 years, pregnancy and admission for acute diabetes complications (ketoacidosis, hyperosmolar coma, hypoglycaemia). Patients admitted with stress hyperglycaemia (17% of total) were also excluded from the study analysis. Clinical records of patients admitted, and meeting inclusion criteria were examined by a diabetes specialist at discharge in order to obtain information on metabolic markers and clinical outcomes and to assess the presence of clinical performance indicators.

The study was conducted according to the guidelines of Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the local Ethics Committee "Comitato Etico Unico per la Provincia di Parma" (Prot.6968, February 21, 2012). All subjects provided written informed consent prior to study entry.

2.2 | Performance metrics and scores

The assessment of clinical management of diabetes was based on a set of clinical performance indicators identified by a panel of diabetes specialists in accordance with National and International recommendations.[13-16]

Five different domains of the inpatient management, which can be retrieved from medical records, were first identified: (a) assessment at admission; (b) glucose monitoring; (c) management of medical therapy; (d) management of consults; (e) management of discharge. Each domain included a number of indicators of clinical process and appropriateness (performance metrics) (Table 1).[17,18] These indicators were used to compute a composite performance score of appropriateness and (presumed) efficacy of inpatient diabetes management. The composite score was generated by assigning a score to each indicator based on the scoring method previously reported by Rossi et al.[19] Specifically, for each item, a score of 1 was assigned when the indicator was recorded/fulfilled, and a score of 0 when the indicator was not detected in the medical records. Therefore, the score of each domain could range from 0 to the maximum number of indicators included in the domain (Table 1). The composite, multi-domain performance score was the sum of the scores of all five domains.

The Charlson comorbidity index (CCI)—which takes into account the number and the severity of comorbid diseases—was calculated as a measure of comorbidity, which is known to predict the risk of short-term mortality in patients enrolled in longitudinal studies.[20]

2.3 | Glucose control intermediate phenotypes and clinical outcomes

Two intermediate metabolic phenotypes were retrieved to be correlated cross-sectionally with the composite performance score:

TABLE 1 Domains, performance metrics and scoring system

Domains	Indicators (performance metrics)	Score
Initial assessment	Record of admission glycaemia	0–5
	Record of fasting plasma glucose	
	Record of HbA1c	
	Appropriate diagnosis of DM	
	Records of history of presence/absence of pharmacological DM therapy	
Glucose monitoring	Appropriate glucose monitoring[a]	0–4
	Presence and use of specific forms for glucose records	
	Presence of clinical protocols to manage hypoglycaemia	
	Presence of clinical protocols to monitor and manage glucose in critically ill patients[b]	
Medical therapy	Record of time of insulin therapy records	0–3
	Record of dose of insulin therapy records	
	Interruption of metformin therapy when indicated[c]	
Management of consults	Diabetes specialist consultation	0–2
	Diabetes nursing consultation	
Management of discharge	Planning of diabetes follow-up visit after discharge	0–3
	Self-glucose monitoring education	
	Diabetes self-management education	

[a]At least 80% of three daily pre-meal glucose testing, or, in critically ill patients, glucose monitoring according to the specific ward protocol.
[b]Patients admitted for acute critical illnesses (ie, myocardial infarction, stroke, septic shock or severe respiratory failure) requiring intensive or semi-intensive therapy and/or, as a rule, not eating during the first 24 to 72 h.
[c]Impaired kidney function, heart failure, hypoxemia, cirrhosis, contrast exposure, surgery and shock.

1 Mean percentage change in glucose levels between plasma glucose at admission and during the last 48 hours before discharge: ([mean glucose at admission-mean glucose at discharge]/ mean glucose at admission) × 100;
2 Achievement of glucose goals (four consecutive pre-meal blood testing ≤130 mg/dL [7.2 mmol/L] or post-prandial ≤180 mg/dL [10 mmol/L], or four consecutive blood testing between 140 and 180 mg/dL [7.8-10 mmol/L] in critically ill patients);

A set of clinical outcomes was retrieved to be correlated cross-sectionally with the composite performance score:

1 Any hypoglycaemia, defined as blood glucose ≤70 mg/dL (3.9 mmol/L)[21]
2 Documented severe hypoglycaemia, (blood glucose ≤40 mg/dL [2.2 mmol/L] with or without clouding of consciousness)
3 Survival rate during hospitalization
4 Discharge condition (a score of 0 was assigned in the event of death or transferral to a ward at higher intensity and a score of 1 in the event of home discharge or transferral to a ward at lower intensity of care)

2.4 | Statistical analysis

Data are presented as means ± SD or median and interquartile range (IQR), where appropriate. To assess differences among wards, ANOVA, χ^2 test and Kruskal–Wallis tests were used.

The cross-sectional associations between performance scores and intermediate phenotypes and clinical outcomes were tested using logistic regression models, in which performance scores along with age, gender, admission glycaemia, ward type, steroid and glucose-lowering therapy and Charlson index were treated as independent variables. A two-stage least squares logistic regression model was performed to investigate the causal relationship between hypoglycaemia and the risk of in-hospital mortality. The explanatory variable was any hypoglycaemia (glucose values <70 mg/dL; 3.9 mmol/L). The instrumental variables were the PS of glucose monitoring, with the addition of age, CCI and steroid and glucose-lowering therapy as confounders.

Statistical analysis was performed using SPSS (IBM SPSS statistics v.22). Statistical significance was set at a two-tailed $P < .05$.

3 | RESULTS

A total of 678 hospitalized patients with diabetes (IMU n = 255, ICU n = 193, GSU n = 230) were enrolled in stage 1 (assessment) of GOVEPAZ.

The main demographic, clinical characteristics and glucose-lowering medications of study subjects admitted in the different wards are reported in Table 2. Mean age was higher in IMU ($P < .0001$) compared with ICU and GSU. Male gender was less prevalent in IMU ($P = .001$). Comorbidity Charlson Index and length of stay were significantly higher in patients admitted to IMU (both $P < .0001$) than those in ICU and GSU. As expected, glucose values at admission

TABLE 2 Demographic, clinical characteristics and glucose-lowering medications of patients admitted in the different wards

	Internal medicine N = 255	Intensive care N = 193	Surgery N = 230	All N = 678	*P* value
Age (yrs)	78 ± 10	74 ± 10	74 ± 10	76 ± 10	<.0001
Gender (Male) (%)	121 (48)	120 (62)	145 (63)	386 (57)	.001
Charlson index	3 (2-4)	2 (1-3)	2 (1-3)	2 (2-4)	<.0001
Length of stay (days)	8 (5-12) 10.2 ± 8.3	6 (4-11) 8.7 ± 8.4	6 (3-11) 9.0 ± 11.9	7 (4-11) 9.4 ± 9.7	<.0001
HbA1c % (mmol/mol)	7.4 (6.5-8) 57.4 (47.9-63.5)	7.2 (6.6-8.3) 55.2 (48.6-67.1)	7.34 (6.5-7.9) 57 (47-63)	7.1 (6.5-8.2) 57 (48-66)	.92
DM duration (yrs)	9 (6-13.8)	8 (6-20)	9 (2.5-11.5)	9 (5-14)	.45
Glucose at admission (mg/dl)	169.5 (126-229)	194 (156-260.5)	147 (117-197)	172 (131-230)	<.0001
Steroid therapy at admission	72 (28.2)	56 (29.0)	21 (9.1)	149 (22.0)	<.0001
Glucose-lowering medications					
None or diet (%)	39 (15.5)	50 (26.4)	30 (13.3)	119 (17.9)	.001
Biguanide (%)	39 (15.5)	22 (11.6)	41 (18.2)	102 (15.3)	.18
Sulfonylurea/glinides (%)	80 (31)	46 (24)	63 (27)	189 (28)	.23
Insulin (%)	87 (34.5)	63 (33.3)	75 (33.3)	186 (27.9)	.95
Others or unknown (%)	7 (2.8)	8 (4.2)	21 (9.3)	16 (2.4)	.08

Note: Data are given as absolute number (%), mean ± SD or median (IQR).

were significantly higher ($P < .0001$) in ICU compared with other settings. Patients were comparable for HbA_{1c} and DM duration among wards.

Steroid therapy at admission was less represented in GSU compared with IMU and ICU settings ($P < .0001$).

Glucose-lowering medications at admission showed a higher frequency of no therapy in ICU compared with the other settings ($P = .001$). No differences were detected in the distribution of glucose-lowering medications among the other settings (Table 2).

3.1 | Performance scores

Total performance score was significantly lower in the GSU compared with the IMU and ICU settings ($P < 0.0001$). The performance scores in the domain of patient's initial assessment and glucose monitoring were statistically lower (both $P < 0.0001$) in GSU compared with IMU and ICU (Table 3). Performance scores were similar across wards in the domains of management of clinical therapy. Performance scores in the domain of management of consults were higher in ICU compared with IMU and GSU wards ($P = .05$), whereas IMU showed higher PS in the domain of management of discharge compared with GSU wards ($P = .003$).

3.2 | Glucose control intermediate phenotypes

The percentage change in glucose values between admission vs the last 48 hours did not differ among wards. Glucose goals during the hospitalization were achieved by 247 (36%) patients, without differences among wards (Table 4).

3.3 | Clinical outcomes

No difference was observed in the number of (severe) hypoglycemic events among wards; 161 patients (26%) experienced at least one hypoglycemic event and 16 patients (2.0%) experienced at least one severe hypoglycemic event.

Survival rate during hospitalization was 95% in the whole cohort, significantly higher in SU (99%) compared with IMU (96%) and ICU (90%) ($P < .0001$).

Patients admitted in IMU and GSU were discharged home more frequently than those admitted in ICU (94% in IMU; 95% GSU and 88% in ICU, respectively, $P < .01$); 7% of all patients experienced a worsening of their clinical condition (deceased or transferred to a higher intensity care ward) (Table 4).

3.4 | Determinants of clinical outcomes

At univariate analysis, clinical outcomes were not influenced by age, gender, CCI and diabetes duration. Glucose values at admission resulted significantly and negatively associated with the achievement of glucose target [OR = 0.998(0.996-1.00) $P = .02$]. Steroid therapy was negatively associated with the achievement of glucose target [OR = 0.86(0.39-0.88), $P = .01$], in-hospital survival (OR = 0.31 [0.15-0.65], $P = .002$) and to a worse discharge condition [OR = 0.34 (0.18-0.64), $P = .001$]. Mean glucose percentage change was significantly affected by glucose level at admission ($\beta = 0.034$, $P = .02$). Glucose-lowering therapy at admission with sulphonylureas/glinides and with insulin was significantly associated with increased risk of hypoglycaemia [OR = 2.45(1.46-4.11)] and [OR = 2.62(1.59-4.31)], respectively. In addition, insulin therapy was negatively associated

TABLE 3 Description of performance scores in the different domains among wards

	Internal Medicine N = 255	Intensive Care N = 193	Surgery N = 230	All N = 678	*P* value
Initial assessment (score 0-5)	4.36 ± 0.69 4 (4-5)	4.38 ± 0.75 5 (4-5)	3.73 ± 0.82 4 (3-4)	4.15 ± 0.81 4 (4-5)	<.0001
Glucose monitoring (score 0-4)	2.99 ± 0.81 3 (2-4)	2.94 ± 0.84 3 (2-4)	2.71 ± 0.78 3 (2-3)	2.88 ± 0.82 3 (2-4)	<.0001
Medical therapy (score 0-3)	2.56 ± 0.72 3 (2-3)	2.54 ± 0.70 3 (2-3)	2.53 ± 0.74 3 (2-3)	2.54 ± 0.72 3 (2-3)	.87
Management of consults (score 0-2)	0.22 ± 0.49 0 (0-0)	0.28 ± 0.50 0 (0-1)	0.19 ± 0.44 0 (0-0)	0.23 ± 0.48 0 (0-0)	.05
Management of discharge (score 0-3)	0.22 ± 0.5 0 (0-0)	0.18 ± 0.46 0 (0-0)	0.12 ± 0.41 0 (0-0)	0.18 ± 0.46 0 (0-0)	.013
Total PS score (score 0-17)	10.4 ± 1.7 10 (9-11)	10.3 ± 1.7 10 (9-11)	9.3 ± 1.6 9 (8-10)	10.0 ± 1.8 10 (9-11)	<.0001

Note: Data are given as mean ± SD and median (interquartile range).

TABLE 4 Glucose intermediate markers and clinical outcomes among wards

	Internal Medicine N = 255	Intensive Care N = 193	Surgery N = 230	All N = 678	*P* value
Mean glucose percentage change (admission–last 48-h) ± SE	40.4 ± 3.7	36.0 ± 1.7	31.2 ± 3.0	36.3 ± 1.8	.11
Glucose target, n (%)	84 (33)	75 (40)	88 (38)	247 (36)	.34
Hypoglycaemia, n (%)	64 (27)	51 (29)	46 (22)	161 (26)	.22
Severe hypoglycaemia, n (%)	7 (3)	5 (3)	4 (2)	16 (2)	.74
Survival rate, n (%)	244 (96)	174 (90)	227 (99)	645 (95)	<.0001
Discharge condition, n (%)	243 (94)	152 (88)	216 (95)	602 (93)	.01

Note: Data are given as n (%) for categorical variables and mean ± SE for continuous variables.

with the achievement of glucose targets [OR = 0.34(0.23-0.52)]. Clinical outcomes were highly dependent on the type of ward. Specifically, in-hospital survival and management of discharge were worse in ICU vs IMU [OR = 0.41 (0.19-0.89); *P* = .02] and OR [0.43 (0.21-0.88), *P* = .001], respectively; whereas GSU ward showed higher but not significant survival rates vs IMU [OR = 2.56(0.69-9.49)].

3.5 | Relationships between performance scores, glucose control intermediate phenotypes and clinical outcomes

To assess whether the performance scores were associated to the glucose intermediate markers and/or to the clinical outcomes, a multivariable regression model was applied to the whole cohort, adjusting for age, gender, CCI, glucose levels at admission, known disease duration and ward type, steroid and glucose lowering therapies (Table 5).

A higher total performance score was directly significantly associated with a higher likelihood of reaching glucose targets [OR = 1.136 (1.013-1.274)] and to an increased survival rate [OR = 1.464 (1.070-2.002)], the latter limited to the IM setting [OR = 2.702 (1.479-4.936)] (Table 5). No other significant associations were evident between total PS and the remaining glucose intermediate phenotypes nor clinical outcomes (Table 5).

We further explored whether the performance scores in the single domains were associated to glucose intermediate markers and/or to clinical outcomes (Table 5). A higher score in the initial assessment was associated with an increased likelihood of reaching glucose targets [OR = 1.45 (1.05-1.98)]. Of note, a higher score in the glucose monitoring domain was associated with a reduced risk of hypoglycemic events [OR = 0.55 (0.41-0.72) *P* < .0001]. This result remained unchanged also after correction for the number of glucose measurements [OR = 0.46 (0.34-0.63) *P* < .0001]. No significant association was found between the performance scores in the domains of management of medical therapy and of discharge and clinical outcomes.

A significant interaction in ward type was observed in the domain of glucose monitoring for survival and management of discharge outcomes; in the IMU ward, the PS in the domain of both glucose monitoring and medical therapy (both *P* for interaction = .005) was positively associated with in-hospital survival: [OR = 6.27 (1.94-20.24) *P* = .002] and [OR = 3.11 (1.26-7.70) *P* = .01], respectively. A higher PS in glucose monitoring resulted also associated with a better management of discharge only in the IMU setting [OR = 2.93 (1.28-6.69), *P* = .01].

TABLE 5 Multivariate logistic regression model for clinical outcomes in the whole population

Performance scores/ OUTCOMES	Hypoglycaemia	Severe hypoglycaemia	Mean glucose percentage change (admission-discharge)	Glucose target	Survival	Discharge condition
Initial assessment score 1	1.09 (0.76-1.56) *P* = 0.64	1.86 (0.59-5.81) *P* = .29	3.57 ± 2.93 *P* = .22	1.45 (1.05–1.98) *P* = .02	1.18 (0.61-2.31) *P* = .63	1.46 (0.82-2.60) *P* = .19
Glucose monitoring score 2	0.55 (0.41-0.72) *P* < .0001	0.68 (0.30-1.51) *P* = .34	−0.55 ± 2.32 *P* = .81	1.19 (0.93-1.51) *P* = .16	1.41 (0.82-2.41) *P* = .21*	1.17 (0.75-1.85) *P* = .49*
Medical therapy score 3	1.17 (0.85-1.62) *P* = .34	0.97 (0.35-2.68) *P* = .95	1.13 ± 2.65 *P* = .67	1.28 (0.99-1.68) *P* = .06	1.33 (0.71-2.49) *P* = .37*	0.98 (0.55-1.73) *P* = .94
Management of consults score 4	1.13 (0.75-1.69) *P* = .56	0.77 (0.17-3.44) *P* = .73	0.38 ± 3.50 *P* = .92	0.95 (0.64-1.40) *P* = .79	3.23 (0.88-11.80) *P* = .08	1.81 (0.72-4.51) *P* = .21
Management of discharge score 5	1.20 (0.79-1.83) *P* = .40	0.98(0.25-3.83) *P* = .98	5.73 ± 3.69 *P* = .12	0.91 (0.61-1.36) *P* = .64	NA	6.38 (0.90-45.48) *P* =0.06
Total performance score	0.94 (0.82-1.07) *P* = .32	0.91 (0.59-1.38) *P* = 0.64	1.11 ± 1.09 *P* = 0.31	1.14 (1.01-1.27) *P* = .03	1.46 (1.07-2.00) *P* = .02*	1.19 (0.94-1.50) *P* = .14

Note: Performance scores along with age, gender, CCI, steroid and glucose lowering therapy, glucose level at admission and ward type entered as predictors. For logistic models are reported OR and 95% CI while for linear regression models beta coefficient and SE. *Significant ward type interaction.

In-hospital mortality was 33/678 (4.9%) with significant differences among wards (33% in IMU, 9% in GSU and 58% in ICU) (*P* < .001).

Hypoglycaemia (also including severe hypoglycaemia) was more frequently associated with in-hospital death (48% vs 25%, *P* = .005) and negatively associated with home-discharge (25% vs 40%).

In multivariable logistic regression models (performance scores in the single domains, age, gender, CCI, steroid and glucose therapy, glucose level at admission and ward type entered as predictors), glucose-lowering therapy with both sulphonylurea/glinides [OR = 2.21 (1.25-3.93) *P* = .007] and insulin [OR = 2.46 (1.39-4.38) *P* = .002] was both independent, positive predictor of hypoglycaemia, whereas only insulin therapy was negatively associated with the achievement of glucose targets [OR = 0.23 (0.14-0.38) *P* < .0001]. Steroid therapy at admission was a negative, independent predictor for the achievement of glucose targets [OR = 0.49 (0.30-0.81) *P* = .006)], in-hospital survival [OR = 0.24 (0.10-0.58) *P* = .001] and a better discharge condition [OR = 0.34 (0.16-0.71) *P* = .004].

Since the PS in glucose monitoring was negatively associated with the risk of hypoglycaemia and positively associated with the likelihood of in-hospital survival, and the relationship with the latter can hardly be underlined by a direct causal role of PS, we exploited the relationship between PS and the risk of hypoglycaemia to explore the hypothesis of a cause-effect relationship between hypoglycaemia and risk of in-hospital death. In a two-stage least squares model for in-hospital survival of the whole cohort using hypoglycaemia as explanatory variable, glucose monitoring performance score as instrumental variable, with the addition of age, CCI, steroid and glucose-lowering therapy as confounders, hypoglycaemia resulted a significant negative predictor of in-hospital survival (β = −0.061, *P* = .04) along with steroid therapy (β = −0.097, *P* < .0001).

4 | DISCUSSION

Stage 1 of GOVEPAZ aimed at developing a composite performance score of quality of diabetes care in non-specialistic inpatient wards and at testing its sensitivity to capture the risk(s) of poor clinical outcome(s) in a cross-sectional setting.

Over one-quarter of hospitalized individuals have diabetes.[2] Despite the large and increasing prevalence of patients with diabetes requiring hospitalization and the robust evidence that there exist a range of in-hospital glucose levels, which is strongly associated to better clinical outcomes, only a very few studies have investigated the flow of clinical milestones of diabetes care as a pre-requisite to achieve better glucose control and, possibly, better clinical outcomes during hospital admissions.[22] This might be partly owed to lack of evaluation tools to assess quality of diabetes care in hospitalized patients. In an attempt to fill this gap, we constructed a composite, multi-domain performance score inspired by the work done by Rossi et al in the QuED and QUASAR study.[19] Differently to the latter, in which main process and intermediate outcome indicators were built to assess the quality of care delivered to people with DM and its long-

term consequences in the outpatient setting, in GOVEPAZ, the performance indicators were tailored for people with diabetes in the inpatient setting.

Our data document that inpatient management of diabetes, as assessed by our performance scores, is heterogeneous across different types of hospital wards and that the performance score(s) of quality of diabetes care: (a) can track variability of glucose-control intermediate phenotypes during hospital admission; and (b) is significantly and independently associated to key clinical endpoints including—but only in the IMU wards—in-hospital mortality (Table 5).

Specifically, despite the robust knowledge that appropriate perioperative assessment and management of glucose can prevent surgical complications—mainly infections—[23]the GSU wards in GOVEPAZ showed a lower overall performance, specifically in pinpointing diabetes at admission and in monitoring and managing glucose dysregulation compared with IMU and ICU settings (Table 4). These data replicate and confirm previously published evidence.[24] In the intensive insulin protocol implementation and outcomes in the medical and surgical wards at a Veterans Affairs Medical Center study, the implementation of a basal-bolus insulin protocol significantly reduced hypoglycemic events, but increased mean blood glucose values. In that study, the lack of adherence to protocol, barriers in overcoming the use of the traditional sliding scale insulin regimens, staff education and change of work-flow habits were suggested as main limiting factors in the achievement of the glucose goals.[24] In GOVEPAZ, the performance scores in the domains of management of consults and discharge were much lower than desirable in all three types of wards, suggesting that, in spite of known diagnosis of diabetes mellitus, the perceived priority of high quality of diabetes care ranks low among health professionals and/or it is not translated in effective work-flow charts (Table 3). Indeed, in a retrospective study conducted in a US academic teaching hospital, diabetes diagnosis was recorded at admission in 96% of patients with pre-existing disease, but daily progress notes mentioned diabetes in only 62% of cases and 60% of discharge notes, and just 20% of discharges indicated a plan for diabetes follow-up.[11] In a National Practice Survey in the US only ~15% of certified diabetes educators reported practicing in an inpatient setting to facilitate transitions and care,[25] despite a consult-based diabetes transition of care service is known to translate into beneficial clinical implications—ie, decreased HbA1c post-discharge—as recently confirmed.[26] The adherence of real world clinical practice to guidelines regarding in-hospital diabetes management is reported to be rather poor. A Spanish survey involving 1000 patients admitted to IMU wards in 111 hospitals across Spain with hyperglycaemia/DM—who were comparable for age, gender, duration of disease and mean HbA_{1c} to our population—showed a low adherence to the standards of diabetes care, starting with major gaps of hyperglycaemia/diabetes indicators in the medical records.[22] In that study only IMU wards were included and a raw, unstructured list of indicators was used without exploring the potential relationship with glucose control intermediate phenotypes and with clinical outcomes during admission. Along the same line, in a study conducted in a US population with diabetes, the compliance of the health professionals to guidelines in insulin prescriptions in IMU wards was 30% even in the presence of computerized protocols.[27] In sharp contrast, a recent Canadian study conducted in a single IMU ward showed a good compliance (80%) to National Guidelines of inpatient diabetes management, which was associated to better glucose control during admission.[28] However, the latter study was monocentric, was conducted in a specialist ward and excluded patients in poor glucose control at admission. The generalization of its findings, therefore, should be cautious.

The type of glucose-lowering medications at admission, namely sulphanilureas/glinides and insulin, were unsurprisingly associated with an increased risk of hypoglycemic events. This study-performed before the widespread use of incretin-based therapy and SGLT2-inhibitors—confirms the detrimental association between iatrogenic hypoglycaemia and adverse clinical outcomes.[29]

In this study, steroid therapy association with worse outcomes may be due to a typical "confound-by-indication" effect, but perhaps also to untoward corticosteroid effects, such as greater susceptibility to infection, fluid retention, hypokalemia, etc. GOVEPAZ was not designed to address these questions.

A major finding of GOVEPAZ is the positive association between performance score(s) and some clinical outcomes (Table 5). A significant positive interaction was evident between higher overall PS and the achievement of glucose goals and, at least limited to IMU ward, in-hospital survival. The significant associations between a higher PS in the domain of glucose monitoring and in the appropriate management of medical therapy with a better survival, restricted to IMU ward, strongly points to a higher capacity of the PS to track clinical outcomes, particularly, in this setting.

Thus, evidence accrued from several sources, including ours, highlights the strong association between appropriate management of diabetes and desirable clinical outcomes. Nevertheless, in our study, the association between PS and clinical outcomes, which stays significant in stage 1 GOVEPAZ even after correcting for age, gender, comorbidities, disease duration, glucose at admission and glucose lowering and steroid therapies, does not necessarily imply a causal relationship, but, for instance, it could simply reflect better ward organization and/or broader competence/attention to the DM status.

Of note, a higher PS in glucose monitoring was independently associated with a ~ 30% reduction in the risk of hypoglycaemia. The latter, in turn, was an independent predictor of in-hospital survival on its own, a finding that has been reported in other studies and highlighted in a recent systematic review.[30,31] Furthermore, severe hypoglycaemia is strongly associated to mortality risk also in the general population of patients with diabetes.[32]

The question arises whether hypoglycaemia per se increases mortality or it is simply an indicator of patient fragility. A randomized controlled trial to address this question would be unethical in humans.

However, in GOVEPAZ, two relevant conditions occurred: (a) The PS of glucose monitoring, which per se has no plausible biologic relationship to mortality, was significantly related to hypoglycaemia, with which a plausible direct relationship can be envisioned; (b) The covariates (age, CCI, steroid therapy) of the risk of in-hospital mortality showed no significant relationship with the PS of glucose

monitoring. Thus, in GOVEPAZ, the conditions to explore a causal relationship between hypoglycaemia and in-hospital mortality through instrumental variable analysis were apparently fulfilled. Our finding that hypoglycaemia was significantly related to the risk of in-hospital mortality in the setting of an instrumental variable analysis strongly supports the existence of a cause-effect relationship between the biology underlying the risk of hypoglycaemia and the in-hospital mortality of patients with diabetes mellitus.

In GOVEPAZ, we used CCI as a measure of comorbidity across the different wards. Indeed, the Charlson index combined with administrative data, age, gender, surgical status has been shown to be as good as other physiology-based scores in predicting in-hospital and long-term mortality in critically ill ICU patients. Other scores (ie, APACHE) might be better predictors of mortality in IC units but their calculation was not possible in all hospitals and settings.[33]

The strengths of stage 1 GOVEPAZ rely on the prospective and multicentre nature of the study, which involved a large number of subjects and three different types of non-specialistic wards. Study limitations should be also acknowledged. Importantly, these data should be interpreted in the frame of our regional health care system and might not be directly extrapolated to other systems of health care delivery. The demonstration of a causal role of hypoglycaemia in the risk of in-hospital death should be replicated in an independent cohort. Finally, mid- and/or long-term clinical outcomes were not investigated.

5 | CONCLUSIONS

Stage 1 GOVEPAZ developed a novel composite, multi-domain performance score of diabetes management in non-specialistic inpatient wards. This performance score highlighted somewhat low compliance to clinical guidelines for diabetes mellitus, especially in the surgery wards. Furthermore, the overall performance score and that of single domains, especially glucose monitoring, were also independently associated to risk of hypoglycaemia and risk of in-hospital death. Further analysis demonstrated that hypoglycaemia may play a causal role in the risk of in-hospital death. Thus, good management of people with DM since the admission may lead to better in-hospital control and overall prognosis by lowering the risk of hypoglycaemia. These results strengthened the rationale for stage 2 of GOVEPAZ, an intervention efficacy study in which an educational intervention is delivered to the health care professionals, aiming at improving the clinical competence and, thereby, the clinical outcomes regarding diabetes in three types of non-specialistic inpatient wards.

ACKNOWLEDGMENTS

The study was funded by Programma di Ricerca RER/-Università 2010-2012-Area 2 Ricerca per il Governo Clinico.

CONFLICT OF INTEREST

ADC has received lecture fees from MSD, AstraZeneca, Eli Lilly, Sanofi, DOC generici, Servier. RA, VR, AVC, FT, DZ, IZ, declare no potential conflicts of interest. VM has received lecture fees from MSD, AstraZeneca, Eli Lilly. RCB has received lecture fees from AstraZeneca, Eli Lilly, Sanofi, MSD, Janssen. RCB has been a board member/advisory panel for Eli Lilly, Sanofi, MSD, Amgen. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Alessandra Dei Cas wrote the draft of the manuscript. Raffaella Aldigeri performed the statistical analyses. Alessandra Dei Cas, Valentina Ridolfi, Ivana Zavaroni, Donatella Zavaroni, Valeria Manicardi, Alessandra Sforza, Anna Vittoria Ciardullo, Franco Tomasi contributed to the writing of the protocol and researched data. Alessandra Dei Cas and Riccardo C. Bonadonna interpreted data and critically revised the manuscript. Alessandra Dei Cas, Raffaella Aldigeri and Riccardo C. Bonadonna are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

GOVERNANCE STUDY GROUP COLLABORATORS

A. Sforza, S. Bianchini; A. Ciardullo, M. Pescetelli; F. Tomasi, A. Carli; V. Manicardi, M. Oliva; I. Zavaroni, V. Ridolfi; G. Mancastroppa, Donatella Zavaroni.

PARTICIPATING CENTERS

Bologna: principal investigator A. Sforza, coinvestigator S. Bianchini; Carpi: principal investigator A. Ciardullo, coinvestigator M. Pescetelli; Ferrara: principal investigator F. Tomasi, coinvestigator *A. Carli*; Montecchio Emilia: principal investigator V. Manicardi, coinvestigator M. Oliva; Parma: principal investigator I. Zavaroni, coinvestigator V. Ridolfi; Piacenza: principal investigator D. Zavaroni, coinvestigator G. Mancastroppa.

ORCID

Alessandra Dei Cas https://orcid.org/0000-0002-8666-4849

REFERENCES

1. Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract*. 2018;138:271-281.
2. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87:978-982.
3. Lucioni C, Garancini MP, Massi-Benedetti M, Mazzi S, Serra G, CODE-2 Italian Advisory Board. The costs of type 2 diabetes mellitus in Italy: a CODE-2 sub-study. CODE-2 Italian advisory board. *Treat Endocrinol*. 2003;2(2):121-133.
4. Evans NR, Dhatariya KK. Assessing the relationship between admission glucose levels, subsequent length of hospital stay, readmission and mortality. *Clin Med (Lond)*. 2012;12(2):137-139.
5. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359-1367.
6. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive Insulin Therapy in the Medical ICU. *N Engl J Med*. 2006;354(5):449-461.
7. Siddiqi L, VanAarsen K, Iansavichene A, Yan J. Risk factors for adverse outcomes in adult and pediatric patients with hyperglycemia

presenting to the emergency department: a systematic review. *Can J Diabetes*. 2018;2671(18):30408-30408. pii: S1499.
8. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ*. 2013;347:f4533.
9. Landstedt-Hallin L, Englund A, Adamson U, Lins PE. Increased QT dispersion during hypoglycaemia in patients with type 2 diabetes mellitus. *J Intern Med*. 1999;246:299-307.
10. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults. *JAMA*. 2008;300(8):933-944.
11. Knecht LA, Gauthier SM, Castro JC, et al. Diabetes care in the hospital: is there clinical inertia? *J Hosp Med*. 2006;3:151-160.
12. Akhter J. The American diabetes Association's clinical practice recommendations and the developing world. *Diabetes Care*. 1997;20:1044-1045.
13. Beltramello G, Manicardi V, Trevisan R. Trialogue: managing hyperglycaemia in internal medicine: instructions for use. *Acta Diabetol*. 2013;50:465-473.
14. Standard italiani per la cura del diabete mellito 2016. www.siditalia.it
15. American Diabetes Association. Standards of medical care in diabetes—2008. *Diabetes Care*. 2008;31(suppl.1):S12-S54.
16. Lansang MC, Umpierrez GE. Inpatient hyperglycemia management: a practical review for primary medical and surgical teams. *Cleve Clin J Med*. 2016;83(5 Suppl 1):S34-S43.
17. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348(5):383-393.
18. Kerr EA, Krein SL, Vijan S, Hofer TP, Hayward RA. Avoiding pitfalls in chronic disease quality measurement: a case for the next generation of technical quality measures. *Am J Manag Care*. 2001;7(11):1033-1043.
19. Rossi MC, Lucisano G, Comaschi M, et al. Quality of diabetes care predicts the development of cardiovascular events: results of the AMD-QUASAR study. *Diabetes Care*. 2011;34(2):347-352.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
21. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;94:709-728.
22. Ena J, Gómez-Huelgas R, Romero-Sánchez M, et al. Hyperglycemia management in patients admitted to internal medicine in Spain: a point-prevalence survey examining adequacy of glycemic control and guideline adherence. *Eur J Intern Med*. 2015;26(6):392-398.
23. Wang YY, Hu SF, Ying HM, et al. Postoperative tight glycemic control significantly reduces postoperative infection rates in patients undergoing surgery: a meta-analysis. *BMC Endocr Disord*. 2018;18(1):42.
24. Chen HJ, Steinke DT, Karounos DG, Lane MT, Matson AW. Intensive insulin protocol implementation and outcomes in the medical and surgical wards at a veterans affairs medical center. *Ann Pharmacother*. 2010;44(2):249-256.
25. Sherr D, Lipman RD. The diabetes educator and the diabetes self-management education engagement: the 2015 National Practice Survey. *Diabetes Educ*. 2015;41(5):616-624.
26. Powers A, Winder M, Maurer M, Brittain K. Impact of inpatient diabetes transitions of care consult on glycemic control. *Patient Educ Couns*. 2020;103(6):1255-1257. https://doi.org/10.1016/j.pec.2020.01.010.
27. Clemens E, Cutler T, Canaria J, Pandya K, Parker P. Prescriber compliance with a new computerized insulin guideline for noncritically ill adults. *Ann Pharmacother*. 2011;45(2):154-156.
28. Alkhiari R, Alzayer H, Aljazeeri J, Vanniyasingam T, Punthakee Z. Guidelines for inpatient pharmacologic Management of Type 2 diabetes in adults and glycemic outcomes. *Can J Diabetes*. 2018;42:158-162.
29. Davis SN, Duckworth W, Emanuele N, et al. Investigators of the veterans affairs diabetes trial. *Diabetes Care*. 2019;42(1):157-163.
30. Carvalho RC, Nishi FA, Ribeiro TB, et al. Association between intrahospital uncontrolled glycemia and health outcomes in patients with diabetes: a systematic review of observational studies. *Curr Diabetes Rev*. 2020. https://doi.org/10.2174/1573399816666200130093523.
31. Nirantharakumar K, Marshall T, Kennedy A, Narendran P, Hemming K, Coleman JJ. Hypoglycaemia is associated with increased length of stay and mortality in people with diabetes who are hospitalized. *Diabetes Med*. 2012;29(12):e445-e448.
32. Jensen MH, Dethlefsen C, Hejlesen O, Vestergaard P. Association of severe hypoglycemia with mortality for people with diabetes mellitus during a 20-year follow-up in denmark: a cohort study. *Acta Diabetol*. 2020;57(5):549–558. https://doi.org/10.1007/s00592-019-01447-x.
33. Christensen S, Johansen MB, Christiansen CF, Jensen R, Lemeshow S. Comparison of Charlson comorbidity index with SAPS and APACHE scores for prediction of mortality following intensive care. *Clin Epidemiol*. 2011;3:203-211.

How to cite this article: Dei Cas A, Aldigeri R, Ridolfi V, et al. A performance score of the quality of inpatient diabetes care is a marker of clinical outcomes and suggests a cause-effect relationship between hypoglycaemia and the risk of in-hospital mortality. *Diabetes Metab Res Rev*. 2020;36:e3347. https://doi.org/10.1002/dmrr.3347