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Clinical Research Article

Implications of an HbA_{1c}-based Diabetes Screening on Prevalence and Effect of Dysglycemia in Patients With COVID-19

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Abstract

Context: In patients with severe acute respiratory syndrome coronavirus type 2 infection, diabetes is associated with poor COVID-19 prognosis. However, case detection strategy is divergent and reported prevalence varies from 5% to 35%.

Objective: We examined how far the choice of screening tools affects the detection rate of dysglycemia and in consequence the estimation of diagnosis-associated risk for moderate (mo) or severe (s) COVID-19.

Methods: Non–intensive care unit inpatients with COVID-19 were screened systematically at admission for diabetes (D) and prediabetes (PreD) by glycated hemoglobin A_{1c} (HbA_{1c}) (A), random blood glucose (B), and known history (C) from November 1, 2020 to March 8, 2021. Dysglycemia rate and effect on COVID-19 outcome were analyzed in 2 screening strategies (ABC vs BC).

Results: A total of 578 of 601 (96.2%) of admitted patients were screened and analyzed. In ABC, prevalence of D and PreD was 38.2% and 37.5%, respectively. D was significantly associated with an increased risk for more severe COVID-19 (adjusted odds ratio [aOR] [moCOVID-19]: 2.27, 95% CI, 1.16-4.46 and aOR [sCOVID-19]: 3.26, 95% CI, 1.56-6.38). Patients with PreD also presented more often with more severe COVID-19 than those with normoglycemia (aOR [moCOVID-19]: 1.76, 95% CI, 1.04-2.97 and aOR [sCOVID-19]: 2.41, 95% CI, 1.37-4.23). Screening with BC failed to identify only 96% of PreD (206/217) and 26.2% of D diagnosis (58/221) and missed associations of dysglycemia and COVID-19 severity.

Conclusion: Pandemic conditions may hamper dysglycemia detection rate and in consequence the awareness of individual patient risk for COVID-19 severity. A systematic diabetes screening including HbA_{1c} reduces underdiagnosis of previously unknown or new-onset dysglycemia, and enhances the quality of risk estimation and access of patients at risk to a diabetes-specific intervention.

Key Words: COVID-19, SARS-CoV-2, prediabetes, diabetes, inflammation, screening

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; aOR, adjusted odds ratio; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; D, diabetes mellitus; EHR, electronic health record; HbA_{1c}, glycated hemoglobin A_{1c}; ICD-10, International Classification of Diseases, revision 10; ICU, intensive care unit; mi, mild; mo, moderate; NoD, normoglycemic; OR, odds ratio; PreD, prediabetes; s, severe; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; sIL2, soluble interleukin receptor 2; SpO_2, oxygen saturation.

In patients with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), diabetes mellitus (D) is associated with a poor prognosis for an adverse outcome of COVID-19 with a nearly 3-fold increased risk of a severe course, need for intensive care unit (ICU) treatment, and mortality (1-3). The degree of hyperglycemia modulates COVID-19 severity. In patients with D, a higher glycated hemoglobin A_{1c} (HbA_{1c}) is associated with increased mortality risk (2, 4). Noteworthy, a higher risk for adverse COVID-19 outcome is also reported for mild forms of dysglycemia such as prediabetes (PreD) (2, 4).

The prevalence of dysglycemia is underreported in Germany, with 1 of 5 D-affected adults in the general population and 1 of 3 inpatient D cases being undiagnosed (5, 6). Furthermore, new-onset D by SARS-CoV-2-infection of pancreatic β cells has been discussed (7) and may also affect future diabetes prevalence in certain populations.

Studies with a divergent choice of case detection strategy report a largely varying prevalence of dysglycemia in COVID-19 patients ranging from 2.4% to 23.9% for PreD and 4.7% to 35.5% for D (1, 8). Surprisingly, prevalence in the examined COVID-19 cohorts was partially even lower

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than in the general population (9). Case detection is the critical starting point for risk estimation analyses and treatment initiation. We hypothesized that in hospitalized patients, systematic screening for diabetes enhances case detection rate affects the estimation of COVID-19 severity and may hence improve access to D-specific management. To evaluate the influence of chosen diagnostic tools on D and PreD prevalence and the associated risk for more severe COVID-19 course, we compared 2 different dysglycemia screening scenarios in a cohort of non-ICU patients with COVID-19 treated at one of the largest COVID-19 university referral centers in Germany.

Materials and Methods

Study Design

This single-center, retrospective study was conducted at the University Hospital Essen, which is located in the Rhine-Ruhr metropolitan area, North Rhine Westphalia, with a catchment area of 5 million residents and that evolved to be one of the largest referral centers for COVID-19 in Germany during the pandemic. As part of the university hospital's quality improvement project SmartDiabetesCare (QiP SDC), a systematic screening for dysglycemia was performed at admission in 4 COVID-19 non-ICU wards from November 1, 2020 until March 8, 2021. Glycemic status obtained by this screening was retrospectively correlated to COVID-19 severity at admission in 2 different scenarios using either all 3 diagnostic tools (ABC strategy) or restricting screening to glucose and known history of PreD/D only (BC strategy). In a subset of patients, immunological and infection-related biomarkers were analyzed and compared to glycemic status.

Informed consent was obtained from all individual participants included in the study. This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the ethics committee of the University Hospital Essen (20-9333-BO).

Description of Patients

Patient cohort

All patients with proven SARS-CoV-2 infection and need of in-hospital treatment at the University Hospital Essen within the study period were included in the analysis. Samples were obtained from the patients' respiratory tract (nasopharyngeal swabs, bronchoalveolar lavage, and endotracheal aspirate) and SARS-CoV-2 RNA was detected using RealStar SARS-CoV-2 RT-PCR (reverse transcription–polymerase chain reaction; Altona Diagnostics) or Abbott RealTime SARS-CoV-2 (Abbott Laboratories) according to the manufacturers' instructions. COVID-19 severity on day of admission was classified in 3 categories according to World Health Organization criteria defining (1) mild disease (miCOVID-19) as a simple infection with COVID-19 without pneumonia; (2) moderate disease (moCOVID-19) as pneumonia with an oxygen saturation (SpO_2) greater than 90% on room air and typical signs such as fever and cough; (3) severe disease (sCOVID-19) as pneumonia with typical symptoms, SpO_2 less than 90% on room air and a respiratory rate greater than 30 breaths per minute or clinical signs of severe dyspnea; and (4) critical COVID-19 disease with need of life-sustaining treatment, such as acute respiratory distress syndrome or septic shock (10). Indication for in-hospital care was made by the departments of infectious diseases and emergency medicine. In general, patients were considered to need in-hospital care if moderate to severe disease was present. The decision for treating patients with miCOVID-19 in hospital was made on an individual basis, for example, in case of relevant comorbidities. Patients presenting at admission with critical disease were directly admitted to the ICU and did not enter the study. Glycemic status, COVID-19 disease severity, chronic kidney disease (CKD, defined by glomerular filtration rate following Kidney Disease: Improving Global Outcomes [KDIGO] criteria), cellular immune status (anti-CD3/CD4/CD8/CD45 antibody, Beckman Coulter catalog No. 6607013, RRID: AB_1575971; https://antibodyregistry.org/search?q=AB_1575973 and anti-CD3/CD19/CD45/CD56 antibody, Beckman Coulter catalog No. 6607073, RRID: AB_1575973; https://antibodyregistry.org/search?q=AB_1575973) and inflammatory markers such as soluble interleukin-2 (sIL2; Siemens catalog No. LKIP1-319, RRID: AB_2904509; https://antibodyregistry.org/search?q=AB_2904509), C-reactive protein (CRP; Siemens, catalog No. 10378883, RRID: AB_2921373), and procalcitonin (Siemens, catalog No. 06522059, RRID: AB_2921372) at admission and body mass index (BMI, documented by nursing staff), were obtained from the electronic health records (EHRs).

Definition of glycemic status

D was defined as HbA_{1c} greater than or equal to 47.5 mmol/mol (6.5%), random plasma glucose greater than or equal to 11.1 mmol/L (200 mg/dL), or known history of D. PreD was defined as HbA_{1c} 38.8 to 46.5 mmol/mol (5.7%-6.4%) and/or known history of PreD. Patients with random plasma glucose less than 11.1 mmol/L (200 mg/dL) and HbA_{1c} less than 38.8 mmol/mol (5.7%) and absence of known history of PreD/D were classified as normoglycemic (NoD). Method of HbA1c measurement fulfilled the standards of "National Glycohemoglobin Standardization Program (NGSP; DCCT-aligned)".

Screening strategy

All patients with proven SARS-CoV-2 infection and need of non-ICU in-hospital treatment at the University Hospital Essen within the observation period were screened for dysglycemia. Patients were asked whether a diagnosis of PreD/D is known. This interview included not only diagnosis of PreD/D, but also current or previous prescription for, indication for, and medication consisting of antidiabetic drugs. Patient declarations were documented in their EHRs. Medical documents provided at admission were screened for evidence of dysglycemia (C1). Furthermore, an algorithm searched each EHR of previous hospital stays for dysglycemia-specific International Classification of Diseases, revision 10 (ICD-10) codes (R.73.0 = PreD; E10-14 = D) (C2). Patient declarations as well as presence of PreD/D-specific ICD-10 codes were classified as positive history of PreD/D (C). Random blood glucose (B) and HbA_{1c} (A) were implemented into the order set of the 4 COVID-19 wards in an opt-out manner, thus patients were biochemically screened for dysglycemia by the first admission blood testing.

Statistical Analysis

Data were analyzed using GraphPad Prism (GraphPad Software Inc) and SPSS 27.0 (IBM Corp) software. Results are shown as mean ± SD and range, median (25th-75th percentile), or absolute number and percentage affected as indicated. A value of *P* less than .05 was considered statistically significant. Laboratory values below and above the detection limit were set to the lower or higher detection limit, respectively.

Prevalence of Dysglycemia

Prevalence of PreD/D was observed in 2 different screening scenarios (ABC vs BC). Multinominal logistic regression analysis was performed to calculate odds ratio (OR) for case identification and 95% CI using a 2-by-2 frequency table. The diagnoses D vs non-D (NoD and PreD) and PreD vs non-PreD (NoD and D), respectively, were used as dependent variables and the screening strategies ABC vs BC as independent variables.

Association analysis of dysglycemia and COVID-19 severity

To assess the association between dysglycemia and COVID-19 severity, multinominal logistic regression analysis was performed to calculate OR and 95% CI using miCOVID-19 vs moCOVID-19 and miCOVID-19 vs sCOVID-19, respectively, as the 2 dependent variables and NoD vs PreD and NoD vs D, respectively, as the 2 independent variables. The analysis was performed unadjusted and adjusted for age and sex, as well as presence of CKD and antihypertensive, lipid-lowering and antidiabetic medication as covariates (adjusted OR; aOR).

Correlation analysis of dysglycemia and immune response

To analyze group differences on immune response in patients with and without dysglycemia, univariate analysis of variance (ANOVA) was computed for continuous variables followed by Bonferroni-corrected post hoc tests. Analyses were performed without adjustment as well as adjusted for age, sex, and presence of CKD and medication of relevant comorbidities (as analysis of covariance, ANCOVA, with age as covariate, and sex and presence of CKD, antihypertensive, lipid-lowering, and antidiabetic medication as between-subject factors). BMI was not considered as a covariate because of a high rate of missing data sets. Kolmogorov-Smirnov test revealed nonnormal distribution for glycemic and immune parameters, which is a prerequisite for parametric tests. However, parametric ANOVA/ANCOVA is assumed to be robust against normality violation if conducted in large samples ($n > 50$) as given in the present data set and, in contrast to nonparametric tests, allows adjustment for confounding factors (11-13). To confirm and extend ANOVA/ANCOVA results, we additionally performed a nonparametric Kruskal-Wallis test to compare patients with NoD, PreD, and D, followed by Bonferroni-corrected post hoc Mann-Whitney *U* tests. To further elucidate the link between glucose metabolism and COVID-19 severity, correlation analysis between parameters of glucose metabolism and immunological and infection-related biomarkers the day of admission were computed as Spearman rho.

Results

Demographic Characteristics

Between November 1, 2020 and March 8, 2021, 601 patients presented with proven SARS-CoV-2 infection and need for in-hospital non-ICU care. In total, 578 of 601 (96.2%) patients were screened and included in the analysis. The majority of patients were men (53.3%) and older than 60 years (67.5%, mean: 66.3 ± 17.4 years). In patients with available BMI (232/578, 40.7%), the majority were overweight or obese (71.1%, mean BMI: 29.0 ± 7.1). Demographic characteristics of the cohort are presented in detail in Supplementary Table S1 (14).

Prevalence of Dysglycemia

HbA_{1c} differed significantly between all patient groups with an increase from NoD to PreD and D. Random glucose was significantly lower in patients with NoD and PreD than in those with D. Patients with NoD were significantly younger than those with PreD and D. In the subgroup with documented BMI, patients with D were more obese than those with NoD or PreD. The 3 patient groups did not differ in sex or prevalence of CKD. Antihypertensive and lipid-lowering medication was significantly more often present in patients with D (Table 1).

Systematic screening using all available D-specific information (ABC) revealed that 3 out of 4 patients with COVID-19 were affected by dysglycemia with a prevalence of PreD and D of 37.5% (217/578) and 38.2% (221/578), respectively (Fig. 1). According to patient declarations, status of PreD/D was unknown before screening in all detected cases with PreD (217/217) and in 31.7% of detected cases with D (70/221). Analysis with stepwise addition of diagnostic tools showed the importance of HbA_{1c} measurement for PreD/D case identification. Asking the patient for known history of PreD/D detected 156 cases, resulting in a dysglycemia prevalence of 27.0%. Expanding screening by an algorithm-based search for dysglycemia-specific ICD-10 codes in previous hospital stays revealed 11 additional cases, resulting in a dysglycemia prevalence of 29.9%. Incorporating information on random blood glucose detected 8 further cases (dysglycemia prevalence of 30.3%). Importantly, the introduction of HbA_{1c} screening identified 263 additional cases, leading to a significant increase in detection rate of PreD/D revealing a dysglycemia prevalence of 75.8% in the entire in-patient COVID-19 cohort. Therefore, the majority of PreD/D cases (428/438, 97.7%) could be identified by HbA_{1c} only (see Fig. 1; Supplementary Table S2) (14). By contrast, restricting diagnostic tools to random glucose and history for PreD/D only (BC strategy) showed a significantly reduced case detection rate, failing to identify 206 of 217 (94.9%) patients with PreD (OR 0.02; 95% CI, 0.01-0.03) and 58 of 221 (26.2%) patients with D (OR 0.26; 95% CI, 0.19-0.34) (Fig. 2).

COVID-19 Severity According to Glycemic Status

In the ABC strategy, patients with PreD showed a higher risk for moCOVID-19 (aOR: 1.76; 95% CI, 1.04-2.97) and sCOVID-19 (aOR: 2.41; 95% CI, 1.37-4.23). Diagnosis of D was associated with a significantly higher risk for moCOVID-19 (aOR: 2.27; 95% CI, 1.16-4.46) and sCOVID-19 (aOR: 3.26; 95% CI, 1.56-6.38) (Fig. 3; Supplementary Table S3) (14).

In the BC strategy, failure to identify patients with PreD and D and misclassifying those cases as NoD significantly increased the percentage of cases with mo/sCOVID-19 in the NoD group (ABC: 62.1 vs BC: 73.2%; $P = .014$). As a consequence, relying on the BC strategy meant that no significant

Table 1. Demographic and COVID-19–related characteristics in hospitalized patients at University Hospital Essen according to glycemic status

Variable	No.	NoD (N = 140)	PreD (N = 217)	D (N = 221)	Results of ANOVA or chi-square test	
					Unadjusted	Adjusted
Age, y	578	$61.7 \pm 22.8^{a,b}$	67.6 ± 16.6^{a}	67.8 ± 13.3^{b}	F = 6.5 *P* = .002	—
Females	578	77 (55.0%)	91 (41.9%)	102 (46.2%)	Chi^2=5.9 *P* = .053	—
CKD	575	50 (36.2%)	60 (27.6%)	77 (35.0%)	Chi^2=3.8 *P* = .15	—
BMI	232	27.3 ± 7.8^{b}	27.5 ± 5.4^{c}	$31.6 \pm 7.7^{b,c}$	F = 9.7 *P* < .001	—
Noninsulin antidiabetic medication	89	0 (0%)^{b}	0 (0%)^{c}	89 (40.3%)^{b,c}	Chi^2 = 162.3 *P* < .0001	
Insulin	80	0 (0%)^{b}	0 (0%)^{c}	80 (36.2%)^{b,c}	Chi^2 = 136.7 *P* < .0001	
Antihypertensive medication	292	54 (38.6%)^{b}	87 (40.1%)^{c}	145 (65.6%)^{b,c}	Chi^2 = 4.8 *P* < .001	—
Lipid-lowering medication	170	27 (19.3%)^{b}	53 (24.4%)^{c}	90 (40.7%)^{b,c}	Chi^2 = 3.0 *P* < .001	
Glucocorticoid medication	40	10 (7.0%)	16 (7.4%)	14 (6.3%)	Chi^2 = .06 *P* = .91	
HbA_{1c}, mmol/mol	578	$34.4 \pm 3.1^{a,b,d,e}$	$42.1 \pm 0.9^{a,c,d,f}$	$55.2 \pm 11.9^{b,c,e,f}$	F = 234.1 *P* < .001	F = 21.1 *P* < .001
HbA_{1c}, %	578	$5.3 \pm 0.5^{a,b,d,e}$	$6.0 \pm 0.3^{a,c,d,f}$	$7.2 \pm 1.3^{b,c,e,f}$	F = 234.1 *P* < .001	F = 21.1 *P* < .001
Glucose, mmol/L	578	$6.5 \pm 2.2^{b,e}$	6.8 ± 2.2^{c}	$8.4 \pm 9.3^{b,c,e}$	F = 23.9 *P* < .001	F = 10.0 *P* < .001
Glucose, mg/dL	578	$117.1 \pm 39.6^{b,e}$	122.5 ± 39.6^{c}	$151.3 \pm 167.6^{b,c,e}$	F = 23.9 *P* < .001	F = 10.0 *P* < .001
Leukocytes, /nL	562	7.2 ± 4.4	7.7 ± 4.6	7.5 ± 4.0	F = 0.49 *P* = .61	F = 0.2 *P* = .85
$CD4^+$ T cells, %	322	41.1 ± 12.8	43.2 ± 14.2	43.3 ± 12.3	F = 1.3 *P* = .28	F = 0.6 *P* = .57
$CD4^+$ T cells, /µL	303	368.7 ± 178.3	395.5 ± 269.9	409.2 ± 239.0	F = 0.6 *P* = .56	F = 0.1 *P* = .95
$CD8^+$ T cells, %	322	$26.5 \pm 12.7^{d,e}$	22.8 ± 13.1^{d}	24.1 ± 10.5^{e}	F = 2.1 *P* = .12	F = 5.8 *P* = .004
$CD8^+$ T cells, /µL	326	228.4 ± 174.3	185.8 ± 135.3	224.8 ± 189.0	F = 2.2 *P* = .11	F = 1.7 *P* = .18
$CD4^+/CD8^+$ ratio	321	$2.1 \pm 1.5^{a,d}$	$3.0 \pm 3.2^{a,d}$	2.5 ± 2.2	F = 3.4 *P* = .036	F = 3.7 *P* = .026
Cytotoxic t cells, %	321	6.0 ± 6.3	5.3 ± 5.5	6.0 ± 5.4	F = 0.6 *P* = .56	F = 0.4 *P* = .67
HLA-DR^+ t cells, %	321	$13.6 \pm 10.4^{d,e}$	11.6 ± 9.3^{d}	12.9 ± 8.7^{e}	F = 1.1 *P* = .33	F = 5.5 *P* = .004
HLA-DR^+ t cells, /µL	326	117.3 ± 133.3^{d}	91.9 ± 73.5^{d}	121.7 ± 132.9	F = 2.4 *P* = .092	F = 3.1 *P* = .048
B lymphocytes, %	321	11.4 ± 9.1	15.0 ± 11.6	13.5 ± 8.9	F = 2.9 *P* = .057	F = 2.5 *P* = .085
B lymphocytes, /µL	325	99.0 ± 104.5	230.1 ± 1146.1	111.8 ± 86.0	F = 1.6 *P* = .20	F = 0.3 *P* = .74
NK cells, %	321	19.1 ± 12.0	18.3 ± 10.7	18.0 ± 9.4	F = 0.3 *P* = .76	F = 0.8 *P* = .47
NK cells, /µL	326	153.2 ± 114.8	156.5 ± 141.0	150.8 ± 109.0	F = 0.1 *P* = .93	F = 1.0 *P* = .38
sIL2, U/mL	418	1123.1 ± 862.1	1311.0 ± 1144.1	1293.9 ± 870.8	F = 1.1 *P* = .32	F = 0.1 *P* = .97

(*continued*)

Table 1. Continued

Variable	No.	NoD (N = 140)	PreD (N = 217)	D (N = 221)	Results of ANOVA or chi-square test	
					Unadjusted	Adjusted
CRP, nmol/L	541	781.0 ± 771.4	781.0 ± 685.7	857.1 ± 704.8	F = 0.92 *P* = .40	F = 0.9 *P* = .40
Procalcitonin, ng/mL	544	0.4 ± 1.2	0.5 ± 1.6	0.9 ± 5.1	F = 1.1 *P* = .34	F = 0.2 *P* = .85

Results are presented as mean ± SD or total number (percentage affected). For continuous variables, *P* values are given as a result of ANOVA tests on the 3 subgroups uncorrected and adjusted for age, sex, and presence of CKD, and antihypertensive, lipid-lowering, and antidiabetic medication. For dichotomous variables, *P* values are given as a result of chi-square tests on the 3 subgroups.
Abbreviations: ANOVA, analysis of variance; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; D, diabetes; HbA_{1c}, glycated hemoglobin A_{1c}; HLA-DR$^+$ cells, human leucocyte antigen DR-positive t-cells; NK cells, natural killer-cells; NoD, no diabetes; PreD, prediabetes; sIL2, soluble interleukin receptor 2.
Equal letters indicate statistically significant differences in Bonferroni-corrected post hoc tests, computed in case of significant results from [a], [b], and [c] uncorrected chi^2/ANOVA and [d], [e], and [f] adjusted ANOVA.

association was found between D status and COVID-19 severity (aOR [mCOVID-19]: 0.96; 95% CI, 0.32-1.53) and (aOR [sCOVID-19]: 0.99; 95% CI, 0.42-1.76). Furthermore, due to the low numbers of identified PreD cases (N = 11; 3 miCOVID-19, 5 moCOVID-19, and 3 sCOVID-19), no OR could be calculated for this patient group in the BC screening strategy (see Fig. 3; Supplementary Table S3) (14).

Markers of Inflammation and Association With Glycemic Status

Association analysis between immunological and infection-related biomarkers and dysglycemia status based on ABC strategy was performed in 321 of 578 COVID-19 patients. CD8+ T cell count was lower in patients with PreD and D than in normoglycemic patients (NoD: 26.5 ± 12.7, PreD: 22.8 ± 13.1; D: 24.1 ± 10.5%; *P* = .004), while CD4$^+$ cells did not differ within groups, resulting in a significantly higher CD4$^+$/CD8$^+$ ratio in patients with PreD and D than in NoD patients (NoD: 2.1 ± 1.5; PreD: 3.0 ± 3.2; D: 2.5 ± 2.2; *P* = .026). HLA-DR$^+$ cell count was lower in patients with dysglycemia in comparison to those without (NoD: 13.6 ± 10.4; PreD: 11.6 ± 9.3; D: 12.9 ± 8.7%; *P* = .004), while numbers of HLA-DR$^+$-cells were lower in patients with PreD compared to NoD and D (NoD: 117.3 ± 133.3; PreD: 91.9 ± 73.5; D: 121.7 ± 132.9/µL; *P* = .048) (see Table 1). Nonparametric testing additionally revealed increased sIL-2 concentrations in patient with D when compared to NoD (NoD: 927 [572-1441]; PreD: 1036 [765-1333]; D: 1097 [760-1561]; *P* = .04). Furthermore, B lymphocyte counts in PreD and D were higher compared to patients with NoD (NoD: 8.7 [5.4-14.3]; PreD: 13.4 [8.4-18.4]; D: 11.2 [6.9-18.8]; *P* = .05), while differences in CD8$^+$ cell count, CD4$^+$/CD8$^+$ ratio, and HLA-DR$^+$ cell counts were no longer statistically significant (Supplementary Table S4) (14). Correlation analysis of COVID-19–related parameters with glycemic status showed associations of small or negligible strength between HbA_{1c} and B lymphocyte count (rho = .11; *P* < .05), HbA_{1c} and

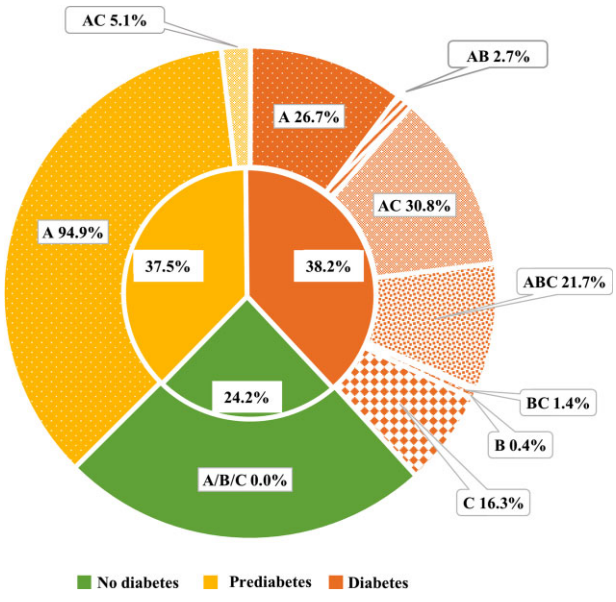

Figure 1. Inner circle: total prevalence of no diabetes (green panel), prediabetes (yellow panel), and diabetes (orange panel) and outer ring: proportion of underlying diagnostic tool (A, HbA_{1c}; B, blood glucose; C, history of diabetes and prediabetes, respectively. AB, HbA_{1c} and blood glucose; AC, HbA_{1c} and history of diabetes and prediabetes, respectively; ABC, HbA_{1c}, blood glucose, and history; BC, blood glucose and history; HbA_{1c}, glycated hemoglobin A_{1c}).

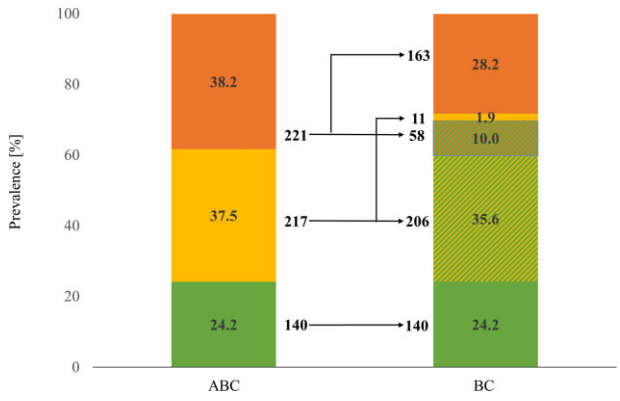

Figure 2. ABC, screening with HbA_{1c}, blood glucose, and history of prediabetes/diabetes; BC, screening with blood glucose and history of prediabetes/diabetes; green panel, no diabetes; yellow panel, prediabetes; orange panel, diabetes; yellow-lined panel, undiagnosed patients with prediabetes; orange-lined panel, undiagnosed patients with diabetes. Data are presented as percentage affected in the bars and in absolute numbers between the bars with arrows indicating change in patients' glycemic status due to choice of diagnostic strategy. HbA_{1c}, glycated hemoglobin A_{1c}.

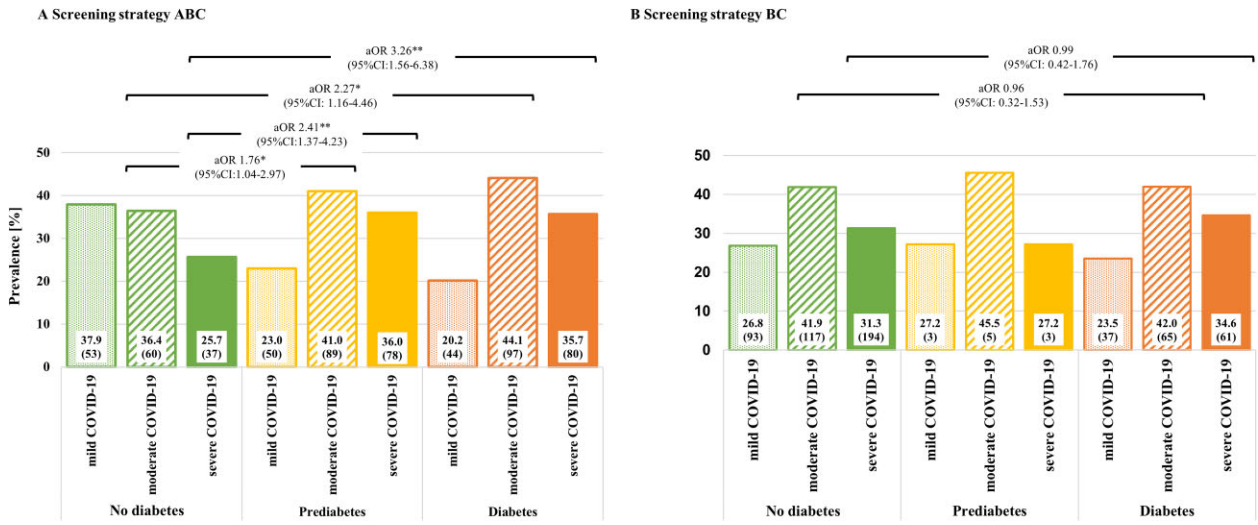

Figure 3. A, ABC-strategy; B, BC-strategy. Data are presented as percentage affected (absolute numbers) and aOR, $*P < .05$, $**P < .01$. In BC-strategy, no analysis was performed in patients with prediabetes due to low number of patients (n = 11 and 3 mild, respectively, 5 moderate and 3 severe cases).

CRP (rho = .09; $P < .05$), as well as between plasma glucose and CRP (rho = 0.13; $P < .05$) (Supplementary Table S5) (14).

Discussion

Summary

In this study, we present the first data on prevalence of PreD and D in a consecutive series of in-hospital, non–ICU-treated patients with COVID-19 obtained by a systematic screening approach. Our study demonstrated a prevalence of 76.7% PreD and D in COVID-19 patients requiring hospitalization. We highlight the relevance of a systematic screening approach per se and the inclusion of HbA_{1c} as diagnostic tool in particular to reduce missed cases, to precisely establish dysglycemia-associated risk, and to illustrate a correlation between COVID-19 severity and degree of dysglycemia.

Relevance of Case Finding Strategy on Prevalence of Dysglycemia in COVID-19

In the literature, the underlying strategy to identify patients with dysglycemia and hence the reported prevalence of D varies. Studies in which diagnoses of diabetes based on diabetes codes documented in national medical databases before or at the study beginning reported that D prevalence in the examined COVID-19 cohort is quite low or ranges at the level of prevalence in the general population with, for example, 2.9% in a British, 10.9% in a US, and 13.7% in a Chinese national registry study (15-17). Hence, the prevalence of D may be underestimated. In Germany, 8.5 million people have known D while another 2 million people are not aware of their diabetic state. Thus, at least 1 of 5 cases of D will be misclassified by using only a known history of D as a diagnostic tool. Similarly, the reported prevalence of undiagnosed D is 18% to 28% in the United Kingdom, 12.5% in the United States, and 27% to 69% in China (18). In addition, cases of new-onset D may be missed by this strategy. Different studies have recently reported new-onset D in 5% to 29% of hospitalized patients with COVID-19 (2, 19-21). On the other hand, studies using HbA_{1c} for case identification reported a high prevalence of PreD and D with 39.4% and 50.2%, respectively, in COVID-19 patients. However, as HbA_{1c} in these studies was obtained based only on the clinical judgment of the attending physician rather than by systematic screening of all COVID-19 patients, dysglycemia prevalence might be overestimated (22). By performing a systematic screening in a large consecutive series of non-ICU in-hospital patients, we demonstrated a high prevalence of PreD and D (37.5% and 38.2%, respectively), with the latter in between reported frequencies in national registry studies and smaller studies of preselected COVID-19 subcohorts. Furthermore, by demonstrating that the majority of patients with dysglycemia (60.3%) would have been misclassified by the less extensive BC strategy, we highlight the importance of an HbA_{1c}-based screening for a thorough and comprehensive PreD/D case detection.

Relevance of Screening Strategy on Severity of COVID-19

Postulating an adverse association between dysglycemia and course of COVID-19, undetected cases with PreD and D erroneously classified as NoD may lead to the underestimation of hyperglycemia-associated risk.

The direct comparison of 2 screening strategies in our cohort underlines the importance of chosen diagnostic tools on risk estimation. In a BC strategy 60.3% of dysglycemia cases were misclassified as normoglycemic. This substantially increased the cases with moCOVID-19 and sCOVID-19 in the NoD group. In consequence, the former with the extended ABC screening–seen association between glucose status and COVID-19 severity would have been missed. In other studies, varying estimation of risk may also be explained by underlying screening strategy. A large meta-analysis of 18 studies in which D diagnosis relied solely on medical history revealed an OR of 1.65 for severe disease in patients with D (23). Using blood glucose in addition to a personal interview and search in electronic medical records in 2 of 3 included cases, Fadini et al (24) reported a D-associated OR of 2.35 for sCOVID-19. Montefusco et al (25) reported an OR of 3.00 for sCOVID-19 in a cohort of D, in which a subset of patients was screened by medical records, blood glucose, and HbA_{1c} at admission (110/551). Restricting HbA_{1c} measurement to

patients who were highly suspected of having D results in an even higher OR of 5.76 for adverse COVID-19, indicating that associated risk might be overestimated in such a case-finding approach (22).

In a meta-analysis strategy report of 6 studies of heterogeneous design, population, and detection, Heidarpour et al (26) found a 2.58 overall OR for sCOVID-19 in patients with PreD with a 1.42 OR in patients detected by fasting glucose and 4.36 OR in preselected patients with HbA_{1c} analysis. By a step-wise screening approach (fasting glucose and medical history in all; HbA_{1c} analysis in only a subset), Li et al (27) reported a hazard ratio of 2.64 for sCOVID-19 in PreD patients, which is in agreement with our findings. However, in our study, PreD was not only prevalent but importantly was also associated with a 1.8- and 2.4-fold increased risk for moCOVID-19 and sCOVID-19, respectively, demonstrating that even seemingly mild forms of hyperglycemia have a negative effect on acute infection with SARS-CoV-2.

The systematic screening approach seems not only to enhance precision on risk estimation but also reveals a continuous increase in COVID severity risk with degree of dysglycemia on admission. This is indicated by an increase of OR from PreD to D for moCOVID-19 and also sCOVID-19 (aOR 1.8-3.3). Our results are underlined by Holman et al (4), who showed that increasing HbA_{1c} was associated with higher mortality risk (hazard ratio 1.22-1.61).

Effect of Prediabetes/Diabetes Diagnosis on Markers of Inflammation

The pathomechanisms contributing to disease severity are not fully understood (28). However, differences regarding immune cell concentration as well as immune response between high- and low-risk individuals have been reported (29). Diabetes-specific data on immunological alterations in COVID-19 are limited. Besides an incapability to control SARS-CoV-2–driven inflammatory responses, failure to respond in a timely fashion to the infection because of a high viral load, delayed type 1 interferon response, but also imbalanced adaptive immunity are discussed as pathomechanisms resulting in sCOVID-19 (28). Data from more than 300 flow cytometry analyses in our COVID-19 cohort obtained at hospital admission indicate that an imbalanced adaption of the immune system may explain the higher risk for an adverse course of COVID-19 in patients with dysglycemia. Patients with PreD/D showed lower $CD8^+$ count and higher $CD4^+/CD8^+$ ratio in line with a study by Sattler reporting an increased $CD4^+/CD8^+$ ratio in patients with COVID-19 and a comorbidity such as diabetes (30). This finding may support the hypothesis of T-cell activation inability as the observed lymphopenia may result in defective T-cell–mediated viral clearance (31). Accordingly, in our study $HLA\text{-}DR^+$ counts were significantly lower in patients with dysglycemia. In the nonparametric analysis, sIL-2 concentration was significantly higher in patients with D. This was found to correlate with the presence of comorbidities and being predictive for indication of ICU treatment and mortality in previous studies (30, 32, 33). Elevation of B-lymphocyte counts in patients with dysglycemia in comparison to normoglycemic patients may reflect plasmablast expansion in the course of polyreactivity following this imbalanced T-cell response (34). However, in our study the significance of results was incongruent in nonparametric and parametric tests, and hence have to be interpreted with caution. By correlation analysis, a positive association between HbA_{1c} and B-lymphocyte count and CRP and random glucose, respectively, and cytotoxic T-cell concentration and CRP was observed; however, this was also of small or negligible strength (rho = 0.09-0.11). Hence, future studies in COVID-19 cohorts will have to explore the precise effect of immune alteration, glucose metabolism, and disease outcome.

Limitations and Strengths of the Study

Unfortunately, BMI documentation was missing in almost 60% of the cohort because of the nursing staff's immense pandemic workload. Therefore, BMI was not considered as a covariate in our analysis. Another potential weakness of our study is the fact that ICD code search in EHRs was limited to our own in-hospital electronic records as no national registry in Germany is available. However, as every single patient was asked and D prevalence in patient interviews is higher than that reported in the general population (35), we assume that patient declarations might be identical to diagnosis documented in outpatient health records. Diagnosis of PreD and D was performed at day 1 of hospital admission. Onset of SARS-CoV-2 symptoms has been found to start 4 to 6 days before (36). Thus, stress-induced hyperglycemia might have evolved in this interval. However, only 3 of 438 patients with D were diagnosed solely by abnormal random glucose measurement. Furthermore, as HbA_{1c} is reported not to be altered by the onset of critical illness (37) and the vast majority of patients with D and all patients with PreD were diagnosed by HbA_{1c} and/or known diagnosis of PreD/D, we assume that stress hyperglycemia was not of significant import. As implementation of SDC QiP was restricted to the non-ICU setting, another limitation is that we did not include patients presenting with critical COVID-19 disease in our analysis. In other studies, 1 of 4 patients with critical disease D was evident as an underlying comorbidity (38, 39). Therefore, it can be speculated that considering the full spectrum of COVID-19 severity at admission might have led to an even higher prevalence of PreD and D and higher risk estimation for severe disease course.

The strength of this study lies in the systematic approach including almost all (96%) patients with COVID-19–related admission in our hospital during the second COVID-19 wave in Germany. As this study was conducted in a hospital dealing with the largest number of COVID-19 patients in Germany since the beginning of the pandemic, we assume that our data obtained in a consecutive manner with almost 600 patients is representative for the German COVID-19 in-hospital population. To our knowledge, the population described in our study is the only in-hospital COVID-19 cohort receiving a complete screening. By analyzing the influence of different diagnostic approaches, we emphasize the relevance of the applied diagnostic tools for identification of PreD and D. Furthermore, our cohort contains not only patients with D but also a large group of patients with PreD showing a clear risk association between seemingly mild dysglycemia and COVID-19 severity.

Conclusion

We demonstrate the need for systematic D screening and the importance of HbA_{1c} measurement for case identification. Systemic screening not only reveals a high prevalence of PreD and D in hospitalized patients with COVID-19 but also establishes precise risk estimation for COVID-19 severity

in this vulnerable patient group, which may greatly benefit from early and dedicated dysglycemia management. Future studies are warranted to examine the benefit of intervention and the level of glycemic control for acute and long-term COVID-19 outcome.

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Author Contributions

S.T. and D.F. are responsible for the study design. L.V.B. and J.R. performed the patient recruitment and data acquisition. L.V.B., J.R., and S.T. wrote the first draft of the manuscript. S.B. and L.V.B. performed the data analysis S.B., A.D., O.W., and D.F. revised the drafts. All authors participated in the writing process by making comments and suggestions and by approving the manuscript. All authors have read and agreed to the content of the manuscript.

Disclosures

L.V.B. and J.R. have nothing to disclose. S.B. has received honoraria and/or expenses for invited speeches from Bayer, Celgene, Janssen-Cilag, Novo Nordisk, Sanofi Aventis, and SymbioPharm. A.D. has received honoraria and/or expenses for invited speeches and/or consultancy from Janssen-Cilag, Boehringer Ingelheim, EIT Health, and face-to-face GmbH. O.W. has received research grants for clinical studies, speaker's fees, honoraria, and travel expenses from Amgen, Alexion, Astellas, Basilea, Biotest, Bristol-Myers Squibb, Correvio, Chiesi, Gilead, Hexal, Janssen, Dr. F. Köhler Chemie, MSD, Novartis, Roche, Pfizer, Sanofi, Takeda, TEVA, and UCB. D.F. has received honoraria and/or expenses for invited speeches from Eisai, Ipsen, and Sanofi Genzyme, is a member of the advisory board of Eisai, Ipsen, and Sanofi Genzyme, and has participated in funded research of Astra Zeneca, Bayer Pharma, Bristol-Myers Squibb, Eiger BioPharmaceuticals, Eli Lilly, Horizon Pharma, Hoffmann-La Roche Ltd, HRA Pharma, Immunovant Sciences GmbH, Incyte Biosciences International Sàrl, Ipsen, Janssen-Cilag GmbH, Lexicon Pharmaceuticals, Madrigal Pharmaceuticals, Novartis, and Otsuka Pharmaceutical. S.T. has received honoraria and/or expenses for invited speeches and/or consultancy from Abbott, Berlin Chemie, Boehringer Ingelheim, BSN Medical, Chugai, Eli Lilly, Falk Foundation, Janssen-Cilag, KWHC, Merck, Nationale Gesundheitsakademie, Nova Biomedical, Novo Nordisk, SciArc and Sanofi-Aventis, and has participated in funded research of ApoScience, Astra Zeneca, Bristol-Myers Squibb, Eiger BioPharmaceuticals, Eli Lilly, Exelixis, Horizon Pharma, Lexicon Pharmaceuticals, Madrigal Pharmaceuticals, Novartis, Novo Nordisk, and Incyte Biosciences International Sàrl.

Data Availability

Some or all data sets generated during and/or analyzed during the present study are not publicly available but are available from the corresponding author on reasonable request.

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