BMJ Open  Imputing HbA1c from capillary blood glucose levels in patients with type 2 diabetes in Sri Lanka: a cross-sectional study


ABSTRACT

Objective To develop a population-specific methodology for estimating glycaemic control that optimises resource allocation for patients with diabetes in rural Sri Lanka.

Design Cross-sectional study.

Setting Trincomalee, Sri Lanka.

Participants Patients with non-insulin-treated type 2 diabetes (n=220) from three hospitals in Trincomalee, Sri Lanka.

Outcome measure Cross-validation was used to build and validate linear regression models to identify predictors of haemoglobin A1c (HbA1c). Validation of models that regress HbA1c on known determinants of glycaemic control was thus the major outcome. These models were then used to devise an algorithm for categorising the patients based on estimated levels of glycaemic control.

Results Time since last oral intake other than water and capillary blood glucose were the statistically significant predictors of HbA1c and thus included in the final models. In order to minimise type II error (misclassifying a high-risk individual as low-risk or moderate-risk), an algorithm for interpreting estimated glycaemic control was created. With this algorithm, 97.2% of the diabetic patients with HbA1c ≥9.0% were correctly identified.

Conclusions Our calibrated algorithm represents a highly sensitive approach for detecting patients with high-risk diabetes while optimising the allocation of HbA1c testing. Implementation of these methods will optimise the usage of resources devoted to the management of diabetes in Trincomalee, Sri Lanka. Further external validation with diverse patient populations is required before applying our algorithm more widely.

BACKGROUND

The global prevalence of diabetes mellitus has rapidly increased and diabetes is now one of the leading causes of morbidity and mortality worldwide. This growing epidemic is straining healthcare systems particularly in low- and middle-income countries (LMICs), where physician shortages and technological constraints are endemic. Sri Lanka, an island nation southeast of India, presents an example of a LMIC experiencing a high burden of type 2 diabetes, health system congestion and technological shortcomings. Rapid, yet accessible, methods of assessing glycaemia are needed to facilitate diabetes care in such clinical settings.

Several clinically validated methods are routinely employed to assess glycaemic control in patients with type 2 diabetes, including haemoglobin A1c (HbA1c), self-monitoring of capillary blood glucose (CBG) and assessment of fasting plasma glucose (FPG). While HbA1c testing is recognised as the standard of care for measuring glycaemic control and is becoming more widely available...
in low- and middle-income settings, patients in Sri Lanka still pay out-of-pocket to obtain HbA1c testing at private laboratory facilities. The World Bank has reported that in 2016, annual per capita healthcare expenditures in Sri Lanka were USD153. HbA1c testing, which costs anywhere between USD22 and USD65 per test, is thus associated with a substantial opportunity cost and most public facilities in rural Sri Lanka lack the financial and human resource capacity to make HbA1c a sustainable marker of glycemic control.\(^6\)\(^7\) Since public subsidisation of diabetes focussed supplies and laboratory services are currently limited to a glucometer, monthly glucometer strips and a CBG measurement at regular appointments, CBG remains the most appropriate method of assessing glycemic control in this population. Previous studies demonstrate significant concordance between HbA1c and CBG: both FPG and post-prandial blood glucose (PPBG) showed strong positive correlations with HbA1c in numerous clinical settings including Sri Lanka.\(^8\)\(^-\)\(^12\) Thus, CBG testing may be an alternative to HbA1c to assess long-term glycemic control in rural Sri Lanka.

The validity of CBG alone to predict HbA1c is, however, controversial, as predicting changes in HbA1c from changes in CBG is not computationally straightforward.\(^13\) Linear regression models are frequently used to impute biomarker levels such as HbA1c from data sets that multidimensionally characterise disease.\(^14\)\(^\)\(^15\) Yet heterogeneous population characteristics present major challenges to validating these models in cohorts with uneven parameter distributions.\(^14\)\(^\)\(^15\) Cross-validation, where multidimensional data sets are divided into evenly sized subsets to train and test regression models, is a common method for generating and validating clinically useful algorithms.\(^16\)\(^17\) The results from algorithm validation are, however, subject to replication instability, where differential sampling uncovers large variation in predictive value.\(^18\)\(^\)\(^19\) Despite such shortcomings, regression models may provide a foundation for rapid and accessible assessment of glycemia in patients with diabetes in Sri Lanka and other LMICs. We report here an alternative method for imputing and interpreting HbA1c from CBG levels within the Tamil population in eastern Sri Lanka that enables providers to rapidly risk-stratify patients with type 2 diabetes, thus reducing the demand for HbA1c testing while ensuring access for high-risk patients.

**MATERIALS AND METHODS**

**Study subjects**

We previously reported the implementation of a model of care that leverages Tamil and Sinhala-speaking medical assistants to address congestion within healthcare settings in Trincomalee, Sri Lanka.\(^20\) For the purposes of this study, we expanded the skillsets of the previously trained medical assistants to include study participant recruitment and HbA1c testing. Recruitment was restricted to patients who met eligibility criteria: (1) confirmed history of type 2 diabetes and (2) not taking insulin. Medical histories and medications of all study participants were verified using medical records and all participants provided written informed consent. Data were obtained for 220 participants across three different hospitals: Trincomalee General Hospital, Selvanayagapuram Hospital and Sampaltheevu Hospital.

**Patient and public involvement**

Study participants consisted of individuals who met eligibility criteria as outlined above. Public involvement for the research was obtained primarily through informing the Eastern Province Health Minister of the study. Participants were not involved in the recruitment, design, conduct, reporting or dissemination plans. Results will be disseminated via channels approved by the Eastern Province Health Minister and presented at national and international conferences.

**Data collection and sampling**

Date of birth, sex, smoking history, duration of diabetes, current diabetes treatment regimen and history of recent hypoglycemic symptoms (nervousness, diaphoresis, tremors and loss of consciousness) were collected for each study participant. Each participant also reported the number of hours since last oral intake other than water. Height, weight, blood pressure and capillary blood specimens were collected from study participants. CBG was measured using a Contour Next Blood Glucose Monitoring System (Bayer), and HbA1c was measured using a DCA Vantage Analyzer (Siemens) imported from the USA, due to local scarcity of HbA1c testing resources. Quality control of both instruments was performed per manufacturers’ specifications. The Bayer Contour Next has been shown to have excellent analytical accuracy.\(^21\) Simple randomisation of the entire study population assigned each participant to either a development cohort (n=110) or a validation cohort (n=110). The demographic characteristics of each cohort were compared using t-tests, \(\chi^2\) tests and Fisher’s exact tests as appropriate. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina) and reported using the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) reporting guidelines.\(^22\)

**Model development and validation**

HbA1c was regressed on each of its potential predictors within the development cohort, including capillary blood glucose, age, sex, body mass index, duration of diabetes and other variables. Capillary blood glucose was the only significant predictor (p<0.05) and was entered in the final model. Participants were stratified by last oral intake to generate models that would account for a patient’s fasting state at the time of sample collection. Two different stratifications were performed to account for: (1) post-prandial glucose physiology and (2) the observed bimodal distribution in hours since last oral intake, with peaks occurring at 3 hours and 13 hours. The first
model stratified participants by last oral intake into three groups (<3 hours, 3 hours to 8 hours and >8 hours since last oral intake) (Model #1), in line with what is known physiologically about postprandial glucose levels. The second model stratified participants by last oral intake into two groups (<8 hours and >8 hours since last oral intake) (Model #2), in line with the bimodal distribution of last oral intake within the study population. Capillary blood glucose cutoffs were calculated from both models that corresponded to each category of last oral intake (see online supplementary appendix A for equations). These cutoffs were then used to categorise glycaemic control according to estimated HbA1c as follows: ‘well-controlled’ (HbA1c ≤7.0%), ‘moderately-controlled’ (HbA1c >7.0 to <9.0%) and ‘poorly-controlled’ (HbA1c ≥9.0%). The predictive value of both models was assessed in the validation cohort by categorising participants by their estimated HbA1c values and their measured HbA1c values and assessing the agreement of the models with the measured HbA1c values. The percent of participants correctly predicted as well as kappa values were calculated as quantitative measures of agreement between models and measured HbA1c values.

HbA1c testing algorithm

Model performance was evaluated post-validation to devise a strategy for identifying individuals who require further HbA1c testing. Our method of categorising participants by estimated glycaemic control necessitates minimising dangerous type II errors (underestimating an individual’s actual risk). Thus, a new HbA1c threshold was determined from the distribution of estimated HbA1c values of participants who were high-risk but misclassified as low-risk. This threshold was applied to an algorithm that categorises participants according to whether they require further HbA1c testing. The development cohort and Model #2 parameters were used to calibrate this algorithm. The predictive value of the recalibrated model was subsequently validated as described above to determine need for further HbA1c testing.

RESULTS

Model development and validation

Table 1 describes demographic data for the combined, development and validation cohorts. None of the variables were significantly different between the development data set and the validation data set. Table 2 shows

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics of combined, development and validation cohorts</th>
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<tbody>
<tr>
<td></td>
<td>Combined (n=220)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60±10</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54 (25%)</td>
</tr>
<tr>
<td>Female</td>
<td>166 (75%)</td>
</tr>
<tr>
<td>Smoking (yes (%))</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Duration of DM (years)</td>
<td>6.5±5.8</td>
</tr>
<tr>
<td>Treatment for DM</td>
<td></td>
</tr>
<tr>
<td>Diet only</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Oral medications</td>
<td>212 (96%)</td>
</tr>
<tr>
<td>Metformin</td>
<td>183 (84%)</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>115 (53%)</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Dipeptidyl peptidase 4 inhibitors</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hypoglycemic symptoms (Yes (%))</td>
<td>112 (51%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26±5</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134±21</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>80±11</td>
</tr>
<tr>
<td>Last oral intake (hours)</td>
<td>7.8±5.2</td>
</tr>
<tr>
<td>Last oral intake</td>
<td></td>
</tr>
<tr>
<td>&lt;3 hours</td>
<td>59 (27%)</td>
</tr>
<tr>
<td>≥3 and≤8 hours</td>
<td>42 (19%)</td>
</tr>
<tr>
<td>&gt;8 hours</td>
<td>119 (54%)</td>
</tr>
<tr>
<td>Capillary blood glucose (mg/dL)</td>
<td>178±80</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3±1.8</td>
</tr>
</tbody>
</table>
last oral intake parameters and glycaemic control categorisations for Model #1 and Model #2. For example, a patient with CBG ≤129 mg/dL who ate <3 hours before testing would be considered ‘well-controlled’ with an estimated HbA1c ≤7.0% using Model #1 parameters. These categorisations allow providers to estimate a patient’s glycaemic control using only capillary blood glucose and time since last oral intake.

Table 3 shows the relationship between actual glycaemic control (categorised by measured HbA1c) and estimated glycaemic control (calculated from the models). Areas highlighted in green represent agreement between the estimated glycaemic control categorisation and the actual glycaemic control categorisation. Areas in white represent disagreement between the estimated glycaemic control categorisation and actual glycaemic control categorisation. In Model #1, 56.3% of participants were correctly categorised (κ=0.2425, 95% CI (0.0959 to 0.3890)). The SE and root mean square error values of the regression model are 0.11 and 1.35 HbA1c percentage points, respectively. In Model #2, 60% of participants were correctly categorised (κ=0.2957, 95% CI (0.1528 to 0.4386)). The SE and root mean square error values of the regression model are 0.11 and 1.40 HbA1c percentage points, respectively. For comparison to other similar models in the literature, we also report the sensitivity and specificity of our models to detect patients whose HbA1c is ≥9%; Model #1 had sensitivity of 50.0% and specificity of 86.5% and Model #2 had a sensitivity of 50.0% and specificity of 89.2%.

Table 2 Categorisations of glycaemic control in Model #1 (left) and Model #2 (right)

<table>
<thead>
<tr>
<th>Time since last oral intake</th>
<th>Model #1</th>
<th>Model #2</th>
</tr>
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<tbody>
<tr>
<td>(Model #1)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;3 hours</td>
<td>≤129 mg/dL</td>
<td>≤117 mg/dL</td>
</tr>
<tr>
<td>3–8 hours</td>
<td>≤105 mg/dL</td>
<td>≤82 mg/dL</td>
</tr>
<tr>
<td>&gt;8 hours</td>
<td>≤82 mg/dL</td>
<td>≤82 mg/dL</td>
</tr>
<tr>
<td>(Model #2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8 hours</td>
<td>≤130–242 mg/dL</td>
<td>≤118–233 mg/dL</td>
</tr>
<tr>
<td>&gt;8 hours</td>
<td>≤106–218 mg/dL</td>
<td>≤83–210 mg/dL</td>
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HbA1c testing algorithm

Online supplementary table S1 (see Appendix B) illustrates the proposed algorithm for identifying individuals who require further HbA1c testing. The algorithm aims to reduce underestimation of risk of inadequate glycaemic control in patients while simultaneously minimising the need for HbA1c testing. Use of this algorithm requires an appropriate HbA1c threshold that minimises both risk underestimation and excessive HbA1c usage. Several potential thresholds were derived from the distribution of estimated HbA1c values among high-risk patients who were incorrectly categorised as low-risk or moderate-risk (n=14).

Online supplementary table S2 (see Appendix B) demonstrates these thresholds as well as their respective type II error rates (the percentage of patients who were high-risk but not grouped as high-risk nor identified for HbA1c testing by the algorithm) and the percentage of the development cohort that would need to have HbA1c testing if that threshold was selected. The optimal balance between type II error rate and total burden of HbA1c testing is with an estimated HbA1c threshold of 7.4% (sample type II error rate of 7.1% while having to perform HbA1c testing on 56.3% of the sample).

The updated algorithm, recalibrated with this threshold presented in table 4, was applied to the validation cohort in order to assess its ability to maintain an acceptable type II error rate while reducing the need for HbA1c testing. Table 5 presents the results of this validation. Only one
high-risk participant out of 36 total high-risk participants would have been placed in the low-risk category and not been identified for further HbA1c testing (type II error rate of 2.8%) with a recalibrated HbA1c threshold of 7.4%. From the 110 participants in the validation cohort, 63 were identified for further testing (57.3%). Of these, 17 (27.0%) were high-risk participants and 46 (73.0%) were non-high-risk participants. In summary, the algorithm correctly identified 97.2% of high-risk individuals either by directly identifying them as high-risk or by identifying them for further testing.

**DISCUSSION AND CONCLUSIONS**

Methods designed to guide the allocation of resources for diabetes management in LMICs like Sri Lanka are necessary due to physician shortages and inadequate resources for routine HbA1c testing. Through the use of regression models and cross-validation, we present an algorithm that detects high-risk individuals either by directly identifying them using random CBG testing or by flagging them for further HbA1c testing. The algorithm had a sensitivity of 97.2% while reducing the number of HbA1c tests by about 40%. The algorithm we devised has two main advantages: (1) it minimises type II errors and (2) it is tailored to the characteristics of high-risk patients. In the setting of Trincomalee, Sri Lanka, where access to HbA1c testing is limited, an HbA1c level of 7.4% was identified for further HbA1c testing while missing very few high-risk patients with type 2 diabetes. This recalibrated threshold allows the algorithm to have the lowest type II error rate for this kind of model observed in the literature. Second, because the algorithm was derived from and validated in the ethnic cohort in which it will be applied, its use is fitted for this particular clinical setting. Racial and ethnic differences in HbA1c have been previously documented, though these differences have an unknown impact on the clinical management of diabetes or the incidence of diabetic complications.

Furthermore, data concerning HbA1c variation between Sri Lankans and internationally accepted HbA1c standards for glycaemic control are sparse. A model that is built specifically for this group is thus clinically advantageous until more is known about the effects of racial and ethnic variation in HbA1c on the clinical management of diabetes.

Although subject recruitment was conducted in a hospital setting, the distinction between the hospital-derived and community-derived patient populations in Sri Lanka must be highlighted. This study is focussed on community derived study subjects waiting in line for their routine checkups at public hospital-based clinics, not the inpatient population where there is a higher likelihood of finding poor glycaemic control and comorbidities in the patient population. In Sri Lanka, patients without financial means to pay for private community clinics or laboratory testing must visit public institutions or smaller provincial facilities for regular diabetes follow-up appointments. Long lines are common in these hospital settings since the traditional outpatient model that is designed to handle this patient population is lacking. As such, the risk profile and comorbidities of this particular hospital-derived patient population closely resembles the general diabetes patient population which would present to the primary care clinics in the community, allowing our model to be generalisable to this rural context. In selecting our patient population for model development, we did not take pre-existing anaemia or chronic kidney disease (CKD) into consideration. While there is some concern that anaemia and CKD may alter the reliability of HbA1c testing, recent research has suggested that this only occurs in patients with severe anaemia and severe CKD. The HbA1c value is unlikely to be altered in patients with mild-to-moderate anaemia and CKD. Given that our patient population in this study resembles the general diabetes population, it is unlikely that severe anaemia and CKD is sufficiently prevalent in this population to have seriously impacted our findings.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Algorithm for decision-making regarding HbA1c testing; updated to reflect chosen HbA1c threshold value of 7.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>If estimated HbA1c &lt;7.4%</td>
<td>If estimated HbA1c 7.4%–8.9% If estimated HbA1c ≥9.0%</td>
</tr>
<tr>
<td>HbA1c Testing</td>
<td>No HbA1c testing needed</td>
</tr>
<tr>
<td>Treatment</td>
<td>Treat as non-high-risk (well-controlled or moderately-controlled according to eHbA1c)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Application of HbA1c testing decision algorithm to validation group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated HbA1c</td>
<td>Actual A1c &lt;9.0%</td>
</tr>
<tr>
<td>&lt;7.4%</td>
<td>21</td>
</tr>
<tr>
<td>7.4%–8.9%</td>
<td>46</td>
</tr>
<tr>
<td>≥9.0%</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
</tr>
</tbody>
</table>

HbA1c, haemoglobin A1c.
Given the small sample size (n=220) and the complex nature of glycaemic control, it is not surprising that only ~60% of participants were correctly categorised by our models into glycaemic control groups and only 50% of patients were correctly identified as having poorly controlled diabetes. The goal of these analyses, however, was not necessarily to eliminate the need for HbA1c testing altogether, but rather to maximise the usage of this limited resource. This can be accomplished by combining the models with the HbA1c threshold algorithm. In spite of the somewhat low predictive value, the sensitivity and specificity of these initial models is comparable to similar models in the literature (sensitivity range 64.5% to 81.8% and specificity range 58.3% to 87%). Many of these other models are comparing predictive value using an HbA1c cut-off of 7.0%, so the lower sensitivity demonstrated by our models (HbA1c cut-off of 9%) is to be expected. A recalibrated algorithm with a threshold of 7.4%, though slightly less stringent than the American Diabetes Association (ADA) guidelines (which state that an HbA1c of <7% is a reasonable target for many non-pregnant adults), ensures that physicians devote their time to engage in a patient-centred care model with patients with diabetes who have the poorest glycaemic control. Indeed, it has been previously suggested that a more appropriate target for glycaemic control may lie between 7% and 8% in most patients with type 2 diabetes. The official recommendation from the Sri Lankan College of Endocrinologists states that an HbA1c of 7.0% is an acceptable glycaemic target for most patients with diabetes. However, their recommendation allows for glycaemic targets ranging from 6.5% to 8% depending on patient comorbidities, age, frequency of hypoglycaemic episodes, duration of diabetes, life expectancy and patient motivation. It has also been demonstrated that individuals with an HbA1c of <7% do not greatly benefit from patient-centred care interventions; rather, individuals with an HbA1c >8.5% are more likely to benefit from a more efficient use of limited resources.

It must be noted that our HbA1c threshold of 7.4% is not a treatment target. Rather, this threshold represents the point at which we can be over 95% confident that a patient with an estimated HbA1c lower than this value is not hyperglycemic and does not have an HbA1c ≥9%. All patients, whether they have an estimated HbA1c higher or lower than 7.4%, will still have a treatment target in line with what is currently known about HbA1c levels and diabetic complications. It should also be emphasised that participants who were categorised as ‘non-high-risk’ by this algorithm still continue to receive high-quality care and monitoring from medical personnel specialising in diabetes care. Risk-stratifying patients by glycaemic control addresses the issue of congestion in the Sri Lankan healthcare system and may optimise the amount of time clinicians spend with their patients. The implications of this new clinical paradigm emphasise a patient-centric approach to achieving adequate glycaemic control while meeting personal health goals. Such a paradigm empowers patients to work with their providers to arrive at an individualised treatment plan, a strategy that is strongly recommended by all major guidelines.

Limitations
Our study cohort of 220 total participants, which were split into two subsets of 110 participants for cross-validation, is relatively small for the generation of this type of regression model. Further studies that incorporate more participants are necessary to further validate these models and resulting algorithm. Furthermore, the scope of our study was restricted to the Tamil population of Trincomalee. It will be necessary to study additional ethnic groups, including the Sinhalese population, in order to generalise our findings. Moreover, an additional analysis that captures patients managed with insulin would further expand our study and allow for the rapid risk stratification of more patients with type 2 diabetes.

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Contributors All authors made significant contributions to the manuscript. MC and GEH are equal contributors. WHH and Aks are equal contributors. MC, GEH, WHH and Aks conceived the study, collected and curated data, performed data analysis, interpreted results and wrote the manuscript. SD helped write the manuscript. LM helped with data analysis. NG and JW provided logistical support and coordinated personnel to facilitate data collection. TJ, AS, and GB facilitated data collection. PK helped interpret results and coordinated personnel to facilitate data collection. UB provided equipment and reagents necessary for data collection and helped interpret results. All authors revised the manuscript for intellectual content. All authors have contributed to and read the manuscript and approved the final copy. We certify that this manuscript is not under review by any other journal.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The University of Michigan Institutional Review Board (IRB) and the Provincial Department of Health Services of the Eastern Province in Sri Lanka reviewed the study (HUM00126960) and determined that it meets criteria for a Quality Assurance/Quality Improvement
initiative aimed at improving pre-existing healthcare delivery. The study was thus deemed outside of the regulatory jurisdiction of the IRB and a waiver was provided.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The de-identified data sets used and/or analysed for this study are available from the corresponding authors on request (wherman@email.umich.edu and asaha@email.umich.edu).

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