Comparing the accuracy of prediction models to detect clinically relevant post-hepatectomy liver failure early after major hepatectomy

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Abstract

Background: Arterial lactate measurements were recently suggested as an early predictor of clinically relevant post-hepatectomy liver failure (PHLF). This needed to be evaluated in the subgroup of major hepatectomies only.

Method: This observational cohort study included consecutive elective major hepatectomies at Karolinska University Hospital from 2010 to 2018. Clinical risk factors for PHLF, perioperative arterial lactate measurements and routine lab values were included in univariable and multivariable regression analysis. Receiver operating characteristics and risk cut-offs were calculated.

Results: In total, 649 patients constituted the study cohort, of which 92 developed PHLF grade B/C according to the International Study Group of Liver Surgery (ISGLS). Lactate reached significantly higher intra- and postoperative levels in PHLF grades B and C compared to grade A or no liver failure (all P < 0.002). Lactate on postoperative day (POD) 1 was superior to earlier measurement time points in predicting PHLF B/C (AUC 0.75), but was outperformed by both clinical risk factors (AUC 0.81, P = 0.031) and bilirubin POD1 (AUC 0.83, P = 0.013). A multivariable logistic regression model including clinical risk factors and bilirubin POD1 had the highest AUC of 0.87 (P = 0.006), with 56.6% sensitivity and 94.7% specificity for PHLF grade B/C (cut-off >0.32). The model identified 46.7% of patients with 90-day mortality and had an equally good discriminatory potential for mortality as the established ISGLS criteria for PHLF grade B/C but could be applied already on POD1.

Conclusion: The potential of lactate to predict PHLF following major hepatectomy was inferior to a prediction model consisting of clinical risk factors and bilirubin on first post-operative day.

Introduction

Post-hepatectomy liver failure (PHLF) is the leading cause of death following liver resection, being involved in 41–62% of postoperative mortality.1–3 In severe PHLF, treatments are limited to supportive measures, and rescue liver transplantation in only very selected cases.4,5 The consensus definition of PHLF by the International Study Group of Liver Surgery (ISGLS) is based on the observation that liver function parameters return to normal values within 5 days after liver resection with a retrospective grading of the clinical severity.6,7 Methods for early identification of patients at high risk for clinically relevant PHLF (ISGLS grades B and C) are needed for estimation of the expected level of care and adequate supportive treatment allocation.

Recently, a multicentre study suggested perioperative lactate measurements as an accurate early diagnostic instrument for identifying patients at risk of clinically relevant PHLF.8 The association of elevated lactate with poor outcome has been studied in different types of liver dysfunction, mainly in acute liver failure and liver transplantation.9–11 Previous studies on liver resections primarily focused on the association between perioperative elevated lactate and postoperative overall morbidity and mortality.12–19 The liver plays an essential role in lactate metabolism because elevated lactate can be caused by either an increased production or a decreased elimination and the liver is involved in both processes.20,21 However, the applicability of lactate for predicting PHLF primarily in major hepatectomies bearing the highest risk of PHLF remains relatively unexplored. Lactate levels seem to depend on the extent of liver resection and the discriminatory potential of lactate measurements could consequently be overestimated in mixed cohorts of both major and minor resections. Moreover, lactate must be put into the context of established pre- and intraoperative clinical risk factors and other routine lab values to assess its additional value for risk prediction.

Thus, the aim of this study was to assess perioperative arterial lactate dynamics, to evaluate lactate in the context of other routine blood tests and clinical risk factors, and to possibly...
develop an early prediction model for clinically relevant PHLF after major liver resection.

**Methods**

In this retrospective single-centre observational cohort study, all consecutive patients undergoing elective major liver resection at Karolinska University Hospital, Stockholm, a Swedish tertiary centre for hepato-pancreato-biliary surgery, from January 2010 to December 2018 were included. All data were extracted from electronic patient charts. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Dnr 2020-04493). The study followed STROBE, TRIPOD and STARD 2015 reporting guidelines.

**Patient characteristics**

The Brisbane 2000 terminology of hepatic anatomy and resections was applied with major resections defined as 3–4 Couinaud segments and extended resections defined as ≥5 Couinaud segments. Exclusion criteria were age younger than 18 years, associating liver partition and portal vein ligation for staged hepatectomy, trauma, liver transplant donation and previous liver transplantation. Assessment for surgery, liver dissection and postoperative care were performed as described earlier. Central venous pressure was lowered to ≤5 mmHg during parenchymal transection. The approach to blood transfusion was increasingly restrictive during the study period. Patients were generally treated with epidural analgesia and a conservative intraoperative fluid strategy was used. The underlying diagnosis and presence of fibrosis/cirrhosis were specified by pathohistological assessment. PHLF was defined and graded according to the ISGLS classification. In case of missing international normalized ratio (INR) and/or serum bilirubin samples on postoperative day (POD) 5, the values on POD4 and POD6 were assessed. Fatal PHLF was defined as death within 90 days following surgery among patients with PHLF grade B/C. The Clavien–Dindo classification was used to evaluate and grade 90-day postoperative complications; grades III–V were summarized as ‘major morbidity’. Postoperative haemorrhage and bile leakage were defined and graded according to the consensus definitions by the ISGLS. The aspartate amino transferase to platelet ratio index and the albumin-bilirubin score were calculated according to established formulas.

**Lactate measurements**

Lactate values were analysed from arterial blood samples (normal range 0.5–2.3 mmol/l (4.5–20.7 mg/dl)). All consecutive available samples from the last preoperative measurement until 24 h after start of surgery were included. Four time points were prespecified for further analysis: the last measurement before start of surgery (lactate preop), highest intraoperative measurement (lactate intraop), first postoperative measurement (lactate postop) and the measurement closest in time to 06:00 on POD1 (lactate POD1). Additionally, the time and level of the highest lactate measurement within 24 h from start of surgery (peak time and peak lactate) were registered.

**Statistical analysis**

Statistical analysis was performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria, packages: gtsummary, ggplot2, ggstatsplot, ggsignif, cutpointtr, pROC).

Descriptive statistics were presented as absolute frequencies and percentages for categorical data and as median and interquartile range for continuous data. Categorical variables were compared using the chi-squared test or Fisher’s exact test. The Kruskal–Wallis rank sum test was used to compare continuous variables between >2 groups and significant results were further analysed by Dunn’s test of multiple comparison with Holm’s correction. P < 0.050 were considered statistically significant.

Previously described and well-established clinical risk factors for PHLF were included in logistic regression modelling. Variables with P<0.200 in univariable logistic regression were included in a multivariable regression model. Backward stepwise selection by Akaike Information Criterion (AIC) was used to identify the most relevant risk factors. To build comparable multivariable logistic regression models for PHLF grade B/C with clinical parameters and one lactate time point each, only patients with available lactate measurements for all four time points were included in the models and compared by AIC. Similarly, the models comparing clinical risk factors, lactate and bilirubin on POD1 were developed in a cohort without missing values for those parameters. Calculation of variance inflation factor and correlation analysis was applied to identify multicollinearity between variables. Presence of influential values was checked by Cook’s distance and scatterplots. As there was no clear linear relationship between the logit of the outcome PHLF B/C and the continuous predictors lactate and bilirubin in the respective multivariable regression models, and both measurements showed a heavily right-skewed distribution, a natural logistic transformation was applied. Necessity of packed red blood cell transfusion was introduced as a binary variable because it did not meet the assumption of linearity with the logit of the outcome. Receiver operating characteristics curves and the respective area under the curve (AUC) were calculated for single predictor variables or multivariable regression models. The F1-score as a combined measurement of sensitivity and positive predictive value (PPV) was used to define optimal cut-offs due to the low incidence of the outcome PHLF B/C.

**Results**

In total, 700 patients underwent elective major liver resections from 2010 to 2018. Exclusion criteria were met by 51 patients, leaving 649 patients in the study cohort. Major morbidity within 90 days following surgery occurred in 238 patients (36%). Overall 90-day mortality corresponding to Clavien–Dindo grade V was 5.3% (34 patients), of which 64.7% (22 patients) were related to PHLF ISGLS grade B/C (fatal PHLF B/C). PHLF occurred in 168 patients (25.9%), and 92 patients (14.2%) had grade B/C liver failure.

**Perioperative lactate dynamics**

Figure 1 shows lactate level dynamics during 24 h from start of surgery in 3 h intervals by ISGLS grade. Patients with PHLF grade A have similar lactate dynamics as patients without liver failure, whereas patients with grades B and C liver failure reach higher and later peak levels. Analysing the prespecified time points, a significant difference appeared intraoperatively between patients without PHLF or grade A in comparison to patients with grades B or C and was maintained following...
surgery until POD1 (all $P < 0.002$; Fig. 2). Although the peak time was reached numerically later in higher grades of PHLF, there was a statistically significant difference only between patients without PHLF and grade C (380 min (95% c.i.: 262–607) versus 623 (95% c.i.: 327–941), $P = 0.018$).

The role of the Pringle manoeuvre in lactate dynamics

Lactate intraop and lactate postop were significantly higher in the subgroup with the Pringle manoeuvre compared to patients without inflow occlusion ($P < 0.001$ and $P = 0.002$, respectively), whereas there was no longer a significant difference in lactate levels on POD1. As a possible consequence of inflow occlusion, in the Pringle subgroup the difference in intraoperative lactate levels between patients with and without PHLF B/C was less significant ($P = 0.002$). However, there was a highly significant difference in lactate levels between patients with and without PHLF B/C following surgery and on POD1 (both $P < 0.001$) in the Pringle subgroup. In the subgroup without the Pringle manoeuvre, the difference in lactate levels between patients with and without PHLF B/C had a high significance level at all three time points ($P < 0.001$).

Lactate and clinical risk factors

The discriminatory potential of each lactate measurement time point for PHLF B/C was highest for lactate POD1 (AUC 0.75 (95% c.i.: 0.69–0.81)), followed by lactate postop (AUC 0.70 (95% c.i.: 0.64–0.77)), peak lactate (AUC 0.70 (95% c.i.: 0.64–0.77)) and lactate intraop (AUC 0.69 (95% c.i.: 0.63–0.76)). By backwards selection the clinical multivariable logistic regression model was reduced to five clinical risk factors: diagnosis, cirrhosis, type of resection, operating time and blood transfusion. Lactate measurement time points were added one at a time to the clinical regression model to evaluate the additional value of lactate for predicting PHLF B/C and compare the different measurement time points (Table S2). Resulting multivariable models showed that underlying gallbladder cancer and perihilar cholangiocarcinoma, cirrhosis, right-sided hepatectomy, operating time, blood transfusion, lactate postop, lactate POD1 and peak lactate were independently associated with PHLF B/C. The model including the five clinical risk factors and lactate POD1 outperformed the other multivariable models by comparison of AIC.

The performance of the lactate cut-offs recommended by Niederwieser et al.\(^8\) in our cohort is shown in Table S3. Applying...
Perioperative lactate levels at prespecified time points

Median lactate levels grouped by post-hepatectomy liver failure (PHLF) grading according to the International Study Group of Liver Surgery at five pre-specified time points, last preoperative (Preop), highest intraoperative (Intraop), first postoperative (Postop), closest to 06:00 on postoperative day (POD) 1 and highest within 24 h from start of surgery (Peak 24 h). Lactate differed significantly between patients without PHLF or grade A compared to grades B or C at all time points except preoperatively. ***P<0.001, **P<0.01, *P<0.05. Whiskers extend to the largest value no further than 1.5 × i.q.r. from the hinge.

Table 1 Multivariable logistic regression models for post-hepatectomy liver failure grade B/C (n = 574)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model clinic</th>
<th>Model clinic + lactate</th>
<th>Model clinic + lactate</th>
<th>Model clinic + bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR</strong></td>
<td><strong>95% c.i.</strong></td>
<td><strong>P</strong></td>
<td><strong>95% c.i.</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CRLM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>0.45</td>
<td>(0.09, 1.67)</td>
<td>0.286</td>
<td></td>
</tr>
<tr>
<td>ICC</td>
<td>0.81</td>
<td>(0.18, 2.60)</td>
<td>0.748</td>
<td></td>
</tr>
<tr>
<td>GBC</td>
<td>3.82</td>
<td>(1.06, 14.1)</td>
<td><strong>0.040</strong></td>
<td></td>
</tr>
<tr>
<td>PCC</td>
<td>3.19</td>
<td>(1.29, 8.00)</td>
<td><strong>0.013</strong></td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>1.60</td>
<td>(0.60, 3.91)</td>
<td>0.319</td>
<td></td>
</tr>
<tr>
<td>Other malign</td>
<td>0.67</td>
<td>(0.15, 2.05)</td>
<td>0.526</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>16.7</td>
<td>(4.54, 73.7)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended right</td>
<td>7.66</td>
<td>(1.80, 48.1)</td>
<td><strong>0.013</strong></td>
<td></td>
</tr>
<tr>
<td>Hemihep left</td>
<td>0.98</td>
<td>(0.13, 7.92)</td>
<td>0.982</td>
<td></td>
</tr>
<tr>
<td>Hemihep right</td>
<td>6.16</td>
<td>(1.40, 39.8)</td>
<td><strong>0.030</strong></td>
<td></td>
</tr>
<tr>
<td>Operating time</td>
<td>1.01</td>
<td>(1.00, 1.01)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td>PRBC transfusion</td>
<td>1.82</td>
<td>(1.03, 3.20)</td>
<td><strong>0.037</strong></td>
<td></td>
</tr>
<tr>
<td>Lactate POD1</td>
<td>3.26</td>
<td>(1.64, 6.65)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td>Bilirubin POD1</td>
<td>5.91</td>
<td>(3.37, 10.9)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td>AIC</td>
<td>392</td>
<td>331</td>
<td>373</td>
<td>341</td>
</tr>
<tr>
<td>AUC (95% c.i.)</td>
<td>0.81 (0.77–0.86)</td>
<td>0.88 (0.84–0.92)</td>
<td>0.84 (0.79–0.89)</td>
<td>0.87 (0.83–0.91)</td>
</tr>
</tbody>
</table>

Lactate and bilirubin measurements were natural log-transformed. CRLM, colorectal cancer liver metastases; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; GBC, gallbladder cancer; PCC, perihilar cholangiocarcinoma; PRBC, packed red blood cells; AIC, Akaike information criterion; AUC, area under the receiver operating characteristic curve. Bold values represents statistically significant.
the suggested definitions of low-risk (NPV $\geq 99.5\%$) and high-risk (maximum F1 score) cut-offs in our cohort results in alternative cut-offs at 0.6 mmol/l and 2.5 mmol/l for lactate POD1 and 1.0 mmol/l and 5.9 mmol/l for peak lactate, respectively.

Predictive potential of perioperative routine lab and bilirubin dynamics

A univariable logistic regression analysis of perioperative routine lab values was performed and among the significant variables, bilirubin POD1 had the highest discriminatory potential for PHLF B/C (AUC 0.84 (95% c.i.: 0.79–0.88); Table S4). Bilirubin differed significantly between patients without PHLF compared to patients with grades A, B and C PHLF preoperatively, at POD1 and POD5 (all $P < 0.001$; Fig. S1).

Multivariable prediction model: clinical risk factors, lactate and bilirubin POD1

Bilirubin and lactate on POD1 were identified as the most relevant blood tests for detection of patients at risk of PHLF B/C, apart from pre- and intraoperative clinical risk factors. Respective multivariable logistic regression models assessing the predictive potential of the different predictor combinations for the main outcome PHLF B/C were built (Table 1, Table S5). Lactate POD1 alone (AUC 0.75 (95% c.i.: 0.69–0.81)) was outperformed by both bilirubin POD1 alone (AUC 0.83 (95% c.i.: 0.78–0.88), $P = 0.013$) and clinical risk factors (AUC 0.81 (95% c.i.: 0.77–0.86), $P = 0.031$; Fig. 3, Table 2). The model including clinical risk factors and bilirubin POD1 had a significantly higher AUC of 0.87 (95% c.i.: 0.83–0.91) than both clinical risk factors alone ($P = 0.006$) or bilirubin POD1 alone ($P = 0.006$), and was not significantly improved by further adding lactate POD1 (AUC 0.88 (95% c.i.: 0.84–0.92), $P = 0.272$).

The optimal cut-off for bilirubin POD1 as the single best biochemical predictor for PHLF B/C defined by maximum F1 score was identified at 44 μmol/l (Table 2). A cut-off at 68 μmol/l was identified for fatal PHLF with an AUC of 0.82 (95% c.i.: 0.71–0.94). In the model with clinical risk factors and bilirubin POD1, a probability of $\geq 0.32$ for PHLF B/C was identified as the optimal cut-off for categorizing patients as high-risk for PHLF B/C (Table 2). With an AUC of 0.88 (95% c.i.: 0.79–0.96), the same model was able to identify patients with fatal PHLF B/C with an optimal cut-off of $\geq 0.62$.

As the proposed prediction models may serve as an early addition to the established ISGLS criteria for PHLF, their performance for identifying other relevant outcomes was compared to the performance of the ISGLS criteria. Of all patients with major morbidity, ISGLS grade B/C was present in 31.3%. In comparison, bilirubin POD1 $\geq 44$ μmol/l identified 26.4% of all patients with major morbidity and the model cut-off of $\geq 0.32$ identified 25.5%. ISGLS grade B/C was present in 60% of
the patients with 90-day mortality. In comparison, bilirubin POD1 ≥ 44 μmol/l had a sensitivity of 43.3% for 90-day mortality and the model cut-off of ≥0.32 had a sensitivity of 46.7%. The discriminatory potential of ISGLS PHLF grade B/C for the outcome major morbidity (AUC 0.63 (95% c.i.: 0.60–0.66)) did not differ significantly from the potential of either bilirubin POD1 (AUC 0.61 (95% c.i.: 0.56–0.66), P = 0.417) or the model with clinical risk factors and bilirubin POD1 (AUC 0.66 (95% c.i.: 0.61–0.70), P = 0.376, Table 2). Likewise, the discriminatory potential of PHLF ISGLS grade B/C for the outcome 90-day mortality (AUC 0.74 (95% c.i.: 0.65–0.83)) did not differ significantly from the potential of either bilirubin POD1 (AUC 0.67 (95% c.i.: 0.56–0.79), P = 0.360) or the model (AUC 0.74 (95% c.i.: 0.64–0.84), P = 0.953), with the advantage of applicability of the latter as early as POD1.

**Discussion**

This study identified bilirubin on POD1, potentially in combination with clinical risk factors, as a more robust early predictor of PHLF within a high-risk cohort exclusively comprised of major hepatectomies, surpassing the predictive capability of lactate measurements.

Arterial lactate is intriguing as an early predictor due to its rapid metabolism. In patients not affected by PHLF, arterial lactate levels increased during surgery, but returned to baseline within 24 h. The same pattern, which can be seen as physiological, could be observed in patients with PHLF grade A, whereas PHLF B/C was associated with higher maximum lactate levels and persisting elevation of lactate beyond 24 h. This strengthens the proposed differentiation between grade A liver failure as a transient situation with outcomes similar to patients without PHLF, versus grades B or C liver failure as ‘clinically relevant’ with severe impact on clinical outcome and, above all, on mortality.35,36

The Pringle manoeuvre partially masked the PHLF B/C-related intraoperative and early postoperative lactate elevation by additionally increasing arterial lactate levels. A marked increase in arterial blood and hepatic venous blood lactate and decrease in hepatic vein oxygen saturation have been shown during the Pringle manoeuvre, indicating the induction of anaerobic glycolysis and thus transforming the liver from a primary lactate consumer to a lactate producer.35,36 Consequently, intraoperative and even early postoperative lactate measurements are less suitable for discriminating development of PHLF B/C when the Pringle manoeuvre is used.

In a recent report by Niederwieser et al., arterial lactate measurements showed excellent discriminatory potential for PHLF B/C in mixed cohorts containing about 45% major hepatectomies, with an AUC of 0.83 and 0.87 for peak lactate and lactate POD1, respectively.8 It is of importance to re-evaluate this information in a cohort of major resections only, which have the highest risk for PHLF. In the present cohort, the performance of lactate for predicting PHLF B/C was substantially lower, with an AUC of 0.70 for peak lactate and an AUC of 0.75 for lactate POD1, as well as considerably different cut-off levels for the suggested risk groups. Similar observations were mentioned in a corresponding subgroup analysis in major hepatectomies by Niederwieser et al.8 Major resection was a strong predictor of elevated lactate POD1 and peak lactate, and it seems that lactate at least partially represents the extent of liver resection23. Thus, lactate has a lower discriminatory and predictive potential for PHLF in major resections where lactate can be elevated due to the reduction of liver size as well as pending liver failure.

Previously well-described pre- and intraoperative clinical risk factors for PHLF were reduced to the most relevant predictors: diagnosis, type of resection, cirrhosis, operating time and blood transfusion. Using lactate and bilirubin for defining postoperative liver dysfunction was previously suggested as part of the Edinburgh criteria. A model including clinical risk factors and bilirubin POD1 resulted in a high discriminatory potential for PHLF B/C in major resections with an AUC of 0.87, which was not further improved by adding lactate POD1. Setting a threshold for the probability of PHLF B/C at ≥0.32 allowed the detection of 56.6% of the patients developing PHLF B/C, with 64.4% of the patients above the cut-off actually developing PHLF B/C later on. As there is currently no causal treatment for PHLF but rescue liver transplantation in selected cases, the most interesting group to identify are patients who develop fatal PHLF B/C. Using the same model, a threshold for the probability of PHLF B/C at ≥0.62 could detect 61.1% of the patients developing fatal PHLF with a PPV of 27.5%. Most importantly, the suggested prediction model had an equally good discriminatory potential for major morbidity and 90-day mortality as the established ISGLS criteria for PHLF grade B/C but can be applied already on POD1. This possibility of early identification of patients at high risk of adverse outcomes could lead to a change in postoperative management and assist in allocating resources to the right patients.

A strength of this study, despite the single-centre setting, is the large and homogenous patient cohort of elective major
hepatectomies. The limitations are due to its retrospective nature, which causes potentially systematical missing lactate measurements in complication-free patients and variation in the exact sampling time point. Another potentially limiting factor is the single-centre design, as local routines for perioperative management may influence the complex metabolism of lactate. Possible relationships between lactate levels, fluid substitution, vasoactive drugs and liver failure will need to be explored separately. The suggested prediction model is not intended for direct clinical implementation. The intention is to highlight the already ongoing transition from a single prognostic biomarker to acknowledging the complexity of PHLF by a more integrative approach with multiparameter models for true implementation of precision medicine.

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Disclosure
The authors declare no conflict of interest.

Supplementary material
Supplementary material is available at BJS online.

Data availability
Derived data supporting the findings of this study are available from the corresponding author (R.B.) on request after appropriate ethical approval.

Author contributions
Ruth Baumgartner (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft, Writing—review & editing), Jennie Engstrand (Conceptualization, Data curation, Methodology, Writing—review & editing), Jonathan Grip (Data curation, Investigation), Patric Rajala (Data curation, Methodology, Writing—review & editing), Poya Ghorbani (Conceptualization, Writing—review & editing), Ernesto Sparrelid (Conceptualization, Methodology, Writing—review & editing) and Stefan Gilg (Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing—original draft, Writing—review & editing).

Previous communication
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