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Complete List of Authors:	Lim, Andy; Monash Health, General Medicine; Monash University, Medicine, School of Clinical Sciences Crnobrnja, Ljiljana; Monash Health, General Medicine Metlapalli, Manogna; Monash Health, General Medicine Jiang, Cathy; Monash Health, General Medicine Wang, Rene; Monash Health, General Medicine Abasszade, Joshua H.; Monash Health, General Medicine
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Title Page

Title:

An Observational Study of the Relative Efficacy of Insulin-glucose Treatment for Hyperkalaemia in Patients with Liver Cirrhosis

Running title:

Insulin-glucose treatment and cirrhosis

Authors:

Andy K.H. Lim [1,2,3]

Ljiljana Crnobrnja [1]

Manogna Metlapalli [1]

Cathy Jiang [1]

Rene Wang [1]

Joshua H. Abasszade [1]

Affiliations:

[1] General Medicine, Monash Health, Clayton, Victoria 3168, Australia.

[2] Nephrology, Monash Health, Clayton, Victoria 3168, Australia.

[3] Department of Medicine, School of Clinical Sciences, Monash University, Clayton, Victoria 3168, Australia.

Corresponding author:

A/Professor Andy Lim

MBBS FRACP MMed(ClinEpi) PhD

Department of General Medicine and Nephrology

Monash Health

246 Clayton Road, Clayton, VIC 3168, Australia

E: andy.lim@monash.edu

T: +61 3 9544 8736

Abstract

Objectives: To determine if liver cirrhosis is associated with reduced efficacy of insulin-glucose treatment in moderate to severe hyperkalaemia.

Design: Retrospective, cohort study.

Setting: Two secondary and one tertiary care hospital at a large metropolitan healthcare network in Melbourne, Australia.

Participants: This study included 465 adults with a mean age of 68.8 ± 15.8 years, comprising 79 patients with cirrhosis and 386 without cirrhosis as controls, who received standard insulin-glucose treatment for a serum potassium ≥6.0 mmol/L from Jan 2017 to Mar 2020. Patients were excluded if they received an insulin infusion, or if there was inadequate follow-up data for at least 6 hours after IDT due to death, loss to follow up, or inadequate biochemistry monitoring. The mean Model for End-stage Liver Disease (MELD) score in patients with cirrhosis was 22.2 ± 7.5, and the distribution of the Child-Pugh score for cirrhosis was: Class A (24%), B (46%), C (30%).

Outcome measures: The primary outcome was the degree of potassium lowering and the secondary outcome was the proportion of patients who achieved normokalaemia, within 6 hours of treatment.

Results: The mean pretreatment potassium for the cohort was 6.57 ± 0.52 mmol/L. After insulin-glucose treatment, mean potassium lowering was 0.84 ± 0.58 mmol/L in patients with cirrhosis compared to 1.33 ± 0.75 mmol/L for controls (p<0.001). The proportion of patients achieving normokalaemia was 33% for patients with cirrhosis, compared to 54% for controls (p=0.001). By multivariable regression, on average, liver cirrhosis was associated with a reduced potassium lowering effect of 0.42 mmol/L (95% CI: 0.25 to 0.59 mmol/L, p<0.001) from insulin-glucose treatment, after adjusting for age, chronic kidney disease, cancer, pretreatment potassium level, β-blocker use, retreatment and cotreatments (sodium polystyrene sulfonate, salbutamol, sodium bicarbonate).

Conclusions: Our observational data suggests reduced efficacy of insulin-glucose treatment for hyperkalaemia in patients with cirrhosis.

Strengths and limitations of this study

- To our knowledge, this is the first study to demonstrate an association between liver cirrhosis and a reduced response to insulin-glucose treatment in hyperkalaemia management in a real-world clinical cohort.
- We used multivariable modelling to account for potential confounding due to age, comorbidities, and concurrent treatments for hyperkalaemia.
- It was a retrospective observational study, and some residual confounding and other treatment biases may not have been fully accounted for.
- Due to the high frequency of cotreatments for hyperkalaemia, the overall potassium lowering effect of insulin-glucose treatment is likely overestimated.

Keywords

Hyperkalemia, potassium, insulin-glucose, insulin-dextrose, cirrhosis, chronic liver disease, efficacy

Word Count

Main text 2924 words, abstract 300 words.

INTRODUCTION

Hyperkalemia is an elevated blood potassium (K^+) level which is associated with the risk of heart rhythm instability that can be fatal. Intravenous insulin-glucose (also known as insulin-dextrose) treatment rapidly lowers blood K^+ by shifting K^+ intracellularly through an indirect effect of activating the cell membrane sodium-K^+ ATPase which then promotes cellular influx of K^+ in exchange for sodium. Insulin-glucose is the preferred treatment for hyperkalemia in the acute setting as methods which enhance K^+ elimination with oral cation exchange resins such as sodium polystyrene sulfonate require many hours or days to be effective. A typical insulin-glucose treatment involves 10 units of regular insulin given intravenously with 25 g of glucose (as intravenous 50 mL of 50% glucose or 50% dextrose).

The efficacy of insulin-glucose shows wide variance such that meta-analysis and pooling of treatment effect has not been possible to date.[1 2] Some of the heterogeneity in reported insulin-glucose efficacy may be due to variations in the study populations and insulin dosing. However, our recent work suggested that specific patient factors may also contribute to this heterogeneity and there was a suggestion that patients with liver cirrhosis may have a modified response to insulin-glucose treatment.[3] Furthermore, there are experimental and observational data showing that patients with liver fibrosis and cirrhosis have insulin resistance, which has an effect on glucose metabolism.[4-6] However, it not clear that K^+ metabolism is altered in patients with cirrhosis, but it is a plausible hypothesis that insulin-glucose may not be as efficacious in patients with cirrhosis compared to patients without cirrhosis in the management of hyperkalaemia.

Hyperkalaemia is a frequent observation in hospitalized patients with cirrhosis, with an estimated prevalence of 12% to 14%.[7] Several observational studies have also found an association between hyperkalaemia and a poorer prognosis and mortality in patients with cirrhosis.[7-9] Thus, it would be important to determine if an established treatment for hyperkalaemia may be compromised in patients with cirrhosis. The aim of this study was to specifically determine if cirrhosis affects the efficacy of insulin-glucose treatment by comparing the K^+ lowering effect of insulin-glucose in patients with and without cirrhosis.

METHODS

Study design and setting

This was a retrospective cohort study of patients who received insulin-glucose treatment at any location (emergency department, inpatient ward, intensive care unit) between Jan 2017 and

Mar 2020, within three major Melbourne metropolitan hospitals (two secondary care and one tertiary care) in a large healthcare network in the state of Victoria, Australia. The healthcare network is the largest public health service in the state, providing healthcare to around one quarter of the population of Melbourne and handling over 260,000 hospital admissions annually.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this study.

Study participants

Only adult patients (≥18 years) with a serum K^+ ≥6.0 mmol/L who received treatment with standard insulin-glucose (intravenous bolus of 10 units of regular insulin with 25 grams of glucose as 50% glucose) were eligible for the study. We used the International Statistical Classification of Diseases and Related Health Problems Tenth Revision (ICD-10) coding to screen for patients with hyperkalaemia. The K^+ levels and insulin-glucose treatment were confirmed by a systematic review of the biochemistry results and medication charts. Assignment to the cirrhosis group is based on an established history of cirrhosis (none of the cases were new diagnoses) and clinical complications of portal hypertension such as encephalopathy, ascites, splenomegaly or varices, or patients with a clear radiological evidence of cirrhosis. Patients with abnormal liver function without clinical or radiological evidence of cirrhosis remained in the control group.

Exclusions

Patients were excluded from the study if they received an insulin and/or glucose infusion instead of standard insulin-glucose, or if there was inadequate follow-up data for at least 6 hours after treatment due to death, loss to follow up, or inadequate K^+ monitoring. The minimum requirement for adequate monitoring to reliably determine the nadir of K^+ is ≥2 biochemistry tests within 6 hours, one of which is within 2 hours of insulin-glucose treatment.

Ethics approval and patient consent

This study was approved by the Monash Health Human Research Ethics Committee (Monash HREC reference: RES-20-0000-604Q-67939). The ethics committee waived individual patient consent due to the retrospective and observational nature of the study, which used data

collected during routine care based on existing treatment protocols. No additional information was sought from patients beyond existing documentation and available laboratory results.

Study outcomes

For the primary outcome, we estimated the change in K^+ (ΔK^+) as the pretreatment K^+ *minus* the posttreatment K^+, thus a negative ΔK^+ value represents the amount of K^+ lowering. The secondary outcome measure was the proportion of patients who achieved normokalaemia (defined as a K^+<5.4 mmol/L) within 6 hours of insulin-glucose treatment, which is the period of protocol monitoring.

Variable definitions

Acute kidney injury (AKI) was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) clinical criteria.[10] Chronic kidney disease (CKD) was defined as a baseline estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.72 m^2 using the CKD-EPI equation, and using a strategy suggested by Siew et al to determine baseline kidney function.[11] We determined the presence of sepsis using the definitions recommended by the Sepsis-3 guidelines.[12] Obesity was defined as a body mass index (BMI) ≥30 kg/m^2 calculated from either measured or self-reported body weight and height. We used the Malnutrition Universal Screening Tool (MUST)[13] score of ≥2 points to define a high risk of malnutrition. Patients were deemed to have active cancer if they had a locally invasive or metastatic solid cancers, or haematological cancer which required chemotherapy, hormonal therapy or immune therapy. This definition excluded patients with a remote history of cancer and patients with cancer who were in remission and no longer receiving active treatment. We report the Model for End-Stage Liver Disease incorporating serum sodium (MELD-sodium) score[14] and the Child-Pugh score[15] as markers for the severity of liver disease for patients with cirrhosis.

Statistical analysis

To examine the association between categorical variables, we used the chi-squared (χ^2) statistic. We used the *t*-test to compare the means of continuous variables between the cirrhosis and control groups. Multivariable linear regression was used to model the association between the ΔK^+ and cirrhosis status. In the initial multivariable model, we included the main epidemiological factor of cirrhosis, potential confounders, variables with a univariable p<0.10, and variables with significant pretreatment differences between the cirrhosis and control groups. Through backwards elimination, we progressed to the final multivariable model and

retained variables with a $p<0.05$ or changed the *b* coefficient for cirrhosis by more than 10%. Statistical interactions between relevant variables were assessed at a 1% level of significance. Multicollinearity was assessed by examining the variance inflation factor. In the final model, multiple imputation was performed for the missing pretreatment blood pH observations, using a linear regression imputation method with 50 imputed datasets. The variables used in the imputation model were age, pretreatment pH, bicarbonate (HCO_3^-) and K^+, cirrhosis, CKD, AKI, cancer, and β-blocker use. Sensitivity analysis was performed by excluding patients who received a second insulin-glucose treatment within the 6-hour monitoring period. When comparing multivariable models and for the sensitivity analysis, we considered a change in the *b* coefficient for cirrhosis of 10% or more as significant. Finally, residual and leverage plots were used to identify outliers and influential observations and the linearity of the continuous independent variables was examined using fractional polynomials. All analyses were performed with STATA version 16 (StataCorp, TX, USA). A $p<0.05$ was considered statistically significant.

RESULTS

Baseline patient characteristics

A total of 79 patients with cirrhosis and 386 patients without cirrhosis (controls) were included in the study (Figure 1). Patients were mostly older (mean age, 69 years) and there was a 2:1 ratio of males to females in the study. Kidney disease was prevalent, with 69% of all patients demonstrating baseline CKD, and 52% of patients suffering from AKI. By comparing patients based on cirrhosis status, both groups were well matched for hospital length of stay, intensive care unit length of stay, requirement for ventilation, rate of AKI and sepsis, diabetes, BMI, malnutrition risk, and active cancer (Table 1). On the other hand, patients with cirrhosis were on average 4.8 years younger than, and there was a smaller proportion of patients with CKD in the cirrhosis group. Patients with cirrhosis were also more likely to be treated with non-selective β-blockers, spironolactone, and trimethoprim-sulfamethoxazole, when compared to controls (Table 1).

Patients with cirrhosis

Of the 79 patients with cirrhosis, the most frequent implicated aetiologies of cirrhosis (non-mutually exclusive) were alcoholic hepatitis (39 of 79 patients, 49.4%), non-alcoholic fatty liver disease (20 of 79 patients, 25.3%), and chronic viral hepatitis (19 of 79 patients, 24.1%).

The less frequent aetiologies (<5%) included drug-induced liver disease, autoimmune hepatitis, cardiac cirrhosis, sclerosing cholangitis and cryptogenic cirrhosis. In terms of the severity of the chronic liver disease, the relative frequency distribution of the Child-Pugh staging of cirrhosis were: Grade A (24.0%), Grade B (45.6%), and Grade C (30.4%). The mean ± standard deviation (SD) of the MELD-sodium score was 22.2 ± 7.5, and the MELD-sodium scores showed a normal distribution. None of the patients with cirrhosis underwent liver transplantation during their index admission.

Biochemistry and cotreatments

The mean ± SD of the pretreatment K^+ levels for the entire cohort was 6.57 ± 0.52 mmol/L. There was a small difference in the mean pretreatment K^+ of 0.13 mmol/L between patients with cirrhosis and controls, which is of uncertain clinical significance. There was also a small difference in mean blood pH of 0.02 which is of uncertain clinical significance, even though serum bicarbonate levels were not different (Table 2). Overall, the mean ΔK^+ was −1.25 mmol/L after insulin-glucose treatment. However, patients with cirrhosis had a smaller ΔK^+ compared to control patients (Table 2 and Figure 2), despite no significant differences in the ΔpH and ΔHCO_3^- levels. Furthermore, the proportion of patients who achieved normokalemia was smaller in patients with cirrhosis compared to control patients (Table 2). In terms of cotreatments, patients with cirrhosis were more likely to receive treatment with sodium polystyrene sulfonate and at higher doses compared to controls. There was also weak evidence that patients with cirrhosis were more likely to receive a repeat insulin-glucose treatment but less likely to receive sodium bicarbonate (Table 2).

Regression of ΔK^+

In the univariable analysis, the *b* coefficient for the regression of ΔK^+ on cirrhosis status was −0.49 (95% CI: −0.67 to −0.32, $p<0.001$). The results of the univariable regression analysis of ΔK^+ on covariates are summarised in Table 3. In the multivariable models, we included the variables which were associated with ΔK^+ or variables which were significantly different in patients with cirrhosis compared to controls. Variables which were not statistically significant or did not show a significant confounding effect were dropped from the model. The results of the multivariable regression models are summarized in Table 4.

After allowing for age, CKD, cancer, pretreatment K^+, β-blocker use, retreatment and cotreatments, the adjusted *b* coefficient for the linear regression of ΔK^+ on cirrhosis status was −0.42 (95% CI: −0.59 to −0.25, $p<0.001$). This was associated with a standardized coefficient

(β) for cirrhosis of 0.21. There was a large overall effect size for the model (η^2=0.28) and the effect size for cirrhosis was considered small-moderate (partial η^2=0.05). On average, the effect of insulin-glucose on ΔK^+ increased with higher pretreatment K^+ levels (*b*=0.63, 95% CI: 0.50 to 0.76, *p*<0.001) but there was no significant interaction between cirrhosis and pretreatment K^+ (*p* for interaction=0.13).

We also conducted sensitivity analyses by excluding patients who received a second insulin-glucose treatment within 6 hours of the initial treatment. Whether or not the multiple regression modelling accounted for baseline blood pH, the changes in the *b* coefficient for cirrhosis status were <10% when patients who received a second insulin-glucose treatment were excluded (Table 4).

DISCUSSION

In this observational study, we sought to determine the real-world clinical significance of insulin resistance in the context of the therapeutic action of insulin in hyperkalemia management. The main finding was that patients with cirrhosis had a decreased response to K^+ lowering by insulin-glucose treatment compared to patients without cirrhosis. We estimated that the magnitude of the difference was 0.42 mmol/L, on average, after adjusting for age, CKD, cancer, pretreatment K^+, β-blocker treatment, and cotreatments. The magnitude of the difference was maintained even after allowing for the pretreatment blood pH and HCO_3^- levels or allowing for the ΔpH and ΔHCO_3^- levels. Similarly, the estimates were unchanged in a sensitivity analysis which excluded patients who received a second insulin-glucose treatment. To our knowledge, this is the first study to demonstrate a reduced efficacy of insulin-glucose treatment for hyperkalemia in patients with established cirrhosis.

Both observational and experimental human studies have demonstrated that insulin resistance and hyperinsulinaemia is common in patients with cirrhosis.[4 16 17 18] Insulin can function to shift both glucose and K^+ into cells, the former through promoting GLUT-4 translocation to the cell membrane in muscle and adipose tissue, and the latter via stimulation of the cell membrane sodium-H^+ antiporter thereby promoting activation of the sodium-K^+ ATPase. However, there is much debate whether glucose and K^+ metabolism can be differentially regulated in the setting of insulin resistance. Observational data suggests that patients with type 2 diabetes and insulin resistance have a higher serum K^+ than patients without insulin resistance.[19] However, experimental data indicates that the effect of insulin on glucose and K^+ can be dissociated.[20 21] Hepatic uptake of K^+ accounts for a significant

proportion of K^+ lowering after an insulin infusion but even cirrhotic livers may retain this function as demonstrated in an in vivo transplantation study.[22] Another speculative hypothesis involves possible alterations in the expression and activity of the sodium-K^+ ATPase in hyperinsulinaemia and insulin-resistant states.[23] Alternatively, some other post-receptor alterations may be contributory in modifying the insulin action on target cells in cirrhosis.[18]

Although the mechanistic explanation for our observation is unclear, others have shown that patients with cirrhosis have a higher serum K^+ in response to oral K^+ loading despite insulin hypersecretion, which was not observed in healthy controls, and in the setting of an equivalent renal K^+ excretion in both groups.[24] Furthermore, we do not believe that the observed difference in K^+ lowering with insulin-glucose treatment can be explained by differences in the acid-base status between the two groups. Neither a drop in blood pH nor serum HCO_3^- were observed in the patients with cirrhosis. Furthermore, both the ΔpH and ΔHCO_3^- were not significantly different between the two groups. Even though the statistical effect size of cirrhosis status on ΔK^+ was only small to moderate in the regression model, the clinical significance of the reduced response to insulin-glucose in patients with cirrhosis was evident by the lower proportion of patients with cirrhosis who achieve normokalaemia compared to controls.

Our findings may be generalized to any adult patient who receives a standard insulin-glucose treatment for hyperkalaemia but may not be valid for patients receiving insulin infusions or other variations in insulin dosing as these patients were explicitly excluded from our study. Most patients with cirrhosis in our study had Child-Pugh B or C cirrhosis and a high MELD-sodium score. Thus, we suggest that the finding of a reduced efficacy of insulin-glucose in lowering K^+ only applies to patients with a clear diagnosis of cirrhosis, particularly those with more advanced cirrhosis.

Study strengths and limitations

To our knowledge, this is the first study to demonstrate an association between liver cirrhosis and a reduced response to insulin-glucose treatment in hyperkalaemia management in a real-world clinical cohort. Another strength is the use of multivariable modelling to account for potential confounding due to age, comorbidities, and concurrent treatments for hyperkalaemia. However, this was a retrospective observational study, and some residual confounding and other treatment biases may not have been fully accounted for. Due to the high frequency of cotreatments for hyperkalaemia, the overall potassium lowering effect of insulin-glucose treatment is likely to be overestimated. Finally, we did not determine if the observed differences in K^+ lowering was associated with any 'hard' adverse outcomes such as arrhythmias or death.

Conclusions

The efficacy of K^+ lowering with insulin-glucose treatment is reduced in patients with cirrhosis when the serum K^+ is 6.0 mmol/L or higher. Therefore, a greater consideration for adjunct treatments for K^+ lowering may be justified in patients with cirrhosis.

Suggestions for further research

A prospective study incorporating an assessment of the degree of insulin resistance (and possibly matching patients with cirrhosis and controls on this variable) and unbiased by cotreatments would provide stronger evidence for a reduced efficacy of insulin-glucose treatment in hyperkalaemia treatment for patients with cirrhosis. An interventional study using different insulin doses may also be useful for finding the insulin dose for patients with cirrhosis which provides the equivalent K^+ lowering effect observed in patients without cirrhosis.

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Competing interests

The authors have no conflict of interests to declare.

Author contributions

A.K.H.L. conceptualized and designed the study. L.C, M.M., C.J., R.W, and J.H.A. reviewed and modified the protocol, and performed data collection. A.K.H.L. performed the analysis and drafted the manuscript. All authors contributed to the review and editing of the final version.

Data sharing statement

The data presented in this study may be available on reasonable request from the corresponding author, subject to approval by the health service research directorate.

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Table 1. Baseline characteristics of patients before insulin-glucose treatment

Characteristic	All patients N = 465	No cirrhosis n = 386	Cirrhosis n = 79	*p*-value
Age, mean (SD), years	68.8 (15.8)	69.6 (16.2)	64.7 (13.0)	0.005
Female, n (%)	174 (37.4)	147 (38.1)	27 (34.2)	0.51
Hospital length of stay, median (IQR), days	7 (3-14)	6 (3-13)	7 (2-17)	0.50
ICU admission, n (%)	135 (29.0)	110 (28.5)	25 (31.7)	0.57
ICU length of stay, median (IQR), hours [1]	69 (40-164)	65 (39-134)	96 (62-176)	0.29
Ventilated, n (%)	69 (14.8)	55 (14.3)	14 (17.7)	0.43
Duration of ventilation, median (IQR), hours [2]	40 (18-134)	37 (15-128)	100 (74-140)	0.12
Acute kidney injury, n (%)	240 (51.6)	193 (50.0)	47 (59.5)	0.12
Sepsis, n (%)	60 (12.9)	47 (12.2)	13 (16.5)	0.30
Body mass index, mean (SD), kg/m^2	28.4 (7.9)	28.3 (7.8)	28.8 (8.2)	0.63
Obese, n (%)	155 (33.6)	130 (34.0)	25 (31.7)	0.68
High malnutrition risk, n (%)	83 (17.9)	66 (17.1)	17 (21.5)	0.35
Diabetes mellitus, n (%)	274 (58.9)	230 (59.6)	44 (55.7)	0.52
Chronic kidney disease, n (%)	319 (68.6)	276 (71.5)	43 (54.4)	0.003
Active cancer, n (%)	78 (16.8)	64 (16.6)	14 (17.7)	0.81
Beta-blockers, n (%)				
β1-selective	169 (36.3)	150 (38.9)	19 (24.1)	<0.001
Non-selective	17 (3.7)	6 (1.6)	11 (13.9)	
ACE inhibitor or ARB, n (%)	157 (33.8)	135 (35.0)	22 (27.9)	0.22
Spironolactone, n (%)				
Low dose (12.5 mg to 50 mg daily)	68 (14.6)	41 (10.6)	27 (34.2)	<0.001
High dose (75 mg to 200 mg daily)	24 (5.2)	1 (0.3)	23 (29.1)	
Trimethoprim-sulfamethoxazole, n (%)	39 (8.4)	26 (6.7)	13 (16.5)	0.005
Subcutaneous insulin, n (%)	114 (24.5)	93 (24.1)	21 (26.6)	0.64
Metformin, n (%)	67 (14.4)	58 (15.0)	9 (11.4)	0.40
Other oral hypoglycemic agents, n (%)				
Sulfonylurea	39 (8.4)	36 (9.3)	3 (3.8)	0.20
Sulfonylurea + gliptin	22 (4.7)	20 (5.2)	2 (2.5)	
Gliptin	33 (7.1)	28 (7.3)	5 (6.3)	
Others	10 (2.2)	8 (2.1)	2 (2.5)	

[1]Only for patients admitted to ICU. [2]Only for patients on ventilation. Abbreviations: ICU, intensive care unit.

Table 2. Biochemistry and hyperkalemia cotreatments by cirrhosis status

Characteristic	All patients N = 465	No cirrhosis n= 386	Cirrhosis n = 79	*p*-value
Pretreatment K^+, mean (SD), mmol/L	6.57 (0.52)	6.59 (0.54)	6.47 (0.41)	0.05
Pretreatment HCO_3^-, mean (SD), mmol/L	20.7 (5.0)	20.8 (5.0)	20.1 (4.6)	0.22
Pretreatment pH, mean (SD) [1]	7.29 (0.09)	7.29 (0.09)	7.31 (0.09)	0.05
Posttreatment K^+, mean (SD), mmol/L	5.32 (0.71)	5.26 (0.71)	5.63 (0.63)	<0.001
Posttreatment HCO_3^-, mean (SD), mmol/L	20.7 (5.0)	20.9 (5.0)	19.7 (4.7)	0.07
Posttreatment pH, mean (SD) [2]	7.30 (0.09)	7.30 (0.08)	7.32 (0.09)	0.05
Change in K^+, mean (SD), mmol/L	−1.25 (0.75)	−1.33 (0.75)	−0.84 (0.58)	<0.001
Change in HCO_3^-, mean (SD), mmol/L	0.07 (2.12)	0.02 (2.16)	0.34 (1.93)	0.21
Change in pH, mean (SD) [3]	0.01 (0.06)	0.01 (0.06)	0.01 (0.04)	0.90
Normokalemia achieved, n (%)	234 (50.3)	208 (53.9)	26 (32.9)	0.001
Cotreatments:				
Repeat insulin-glucose <6 h, n (%)	93 (20.0)	71 (18.4)	23 (27.9)	0.06
Repeat interval, mean (SD), min [4]	184 (94)	183 (94)	188 (97)	0.86
Sodium polystyrene sulfonate, n (%)	294 (63.2)	236 (61.1)	58 (73.4)	0.04
15 grams	56 (12.0)	47 (12.2)	9 (11.4)	
30 to 60 grams	238 (51.2)	189 (49.0)	49 (62.0)	
Salbutamol, n (%)	54 (11.6)	49 (12.7)	5 (6.3)	0.11
Sodium bicarbonate, n (%)	47 (10.1)	42 (10.9)	5 (6.3)	0.07
<100 mmol	23 (5.0)	18 (4.7)	5 (6.3)	
≥100 mmol	24 (5.2)	24 (6.2)	0 (0)	

[1] missing observations = 71 (15.3%).
[2] missing observations = 44 (9.5%).
[3] missing observations = 80 (17.2%).
[4] patients who received a second insulin-glucose treatment only.

Table 3. Univariable linear regression

Variable	*b*	(95% CI)	*p*-value
Cirrhosis	−0.49	(−0.67 to −0.32)	**<0.001**
Age, per 10 years	−0.04	(−0.09 to −0.00)	**0.046**
Female sex	0.01	(−0.13 to 0.16)	0.84
Diabetes	−0.02	(−0.16 to 0.12)	0.80
Insulin-requiring diabetes	−0.04	(−0.20 to 0.12)	0.65
Body mass index, per 5 kg/m^2	−0.02	(−0.07 to 0.02)	0.29
Chronic kidney disease	−0.08	(−0.23 to 0.06)	0.27
Active cancer	−0.17	(−0.35 to 0.01)	**0.069**
High malnutrition risk [1]	0.11	(−0.07 to 0.29)	0.22
Sepsis	−0.08	(−0.29 to 0.12)	0.42
Acute kidney injury	0.00	(−0.14 to 0.14)	0.99
Beta-blockers			
Cardioselective	0.10	(−0.04 to 0.25)	0.36
Non-selective	0.06	(−0.31 to 0.42)	
Pretreatment K^+	0.61	(0.50 to 0.74)	**<0.001**
Pretreatment HCO_3^-	0.01	(−0.01 to 0.02)	0.31
Pretreatment pH	0.01	(0.83 to 0.85)	0.98
Repeat insulin-glucose	−0.07	(−0.24 to 0.10)	0.42
Sodium polystyrene sulfonate	−0.22	(−0.36 to −0.08)	**0.003**
Salbutamol	0.27	(0.06 to 0.48)	**0.012**
Sodium bicarbonate			
<100 mmol	−0.04	(−0.35 to 0.27)	**0.002**
≥100 mmol	0.55	(0.24 to 0.85)	

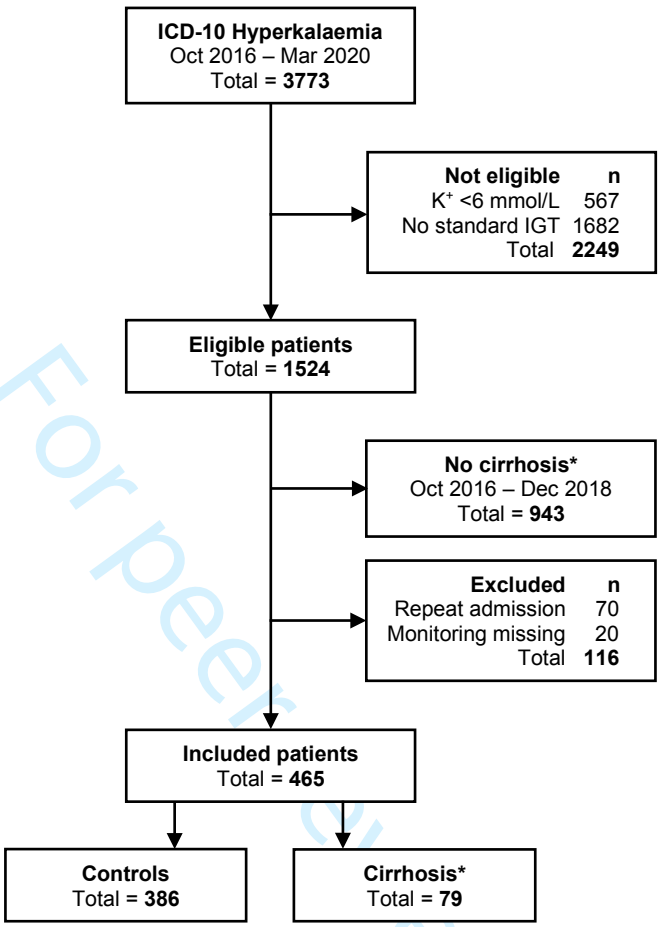
[1] Malnutrition Universal Screening Tool (MUST) score ≥2.

Table 4. Coefficient for cirrhosis under different multiple regression models

Model	Cirrhosis *b* (95% CI)	Δ *b*
Univariable regression on cirrhosis	−0.49 (−0.67 to −0.32)	
Model 1: Adjusted for age, pretreatment K^+, chronic kidney disease, active cancer, beta-blocker use, and cotreatments (*n*=465)	−0.42 (−0.59 to −0.25)	+15.3% [1]
Model 2: Adjusted for Model 1 covariates and the pretreatment pH levels (*n*=465)	−0.43 (−0.59 to −0.26)	−2.2% [2]
Model 3: Sensitivity analysis, Model 1 covariates excluding patients who received repeat insulin-glucose treatment (*n*=372)	−0.38 (−0.58 to −0.18)	+9.4% [2]
Model 4: Sensitivity analysis, Model 2 covariates excluding patients who received repeat insulin-glucose treatment (*n*=372)	−0.40 (−0.60 to −0.21)	+5.5% [3]

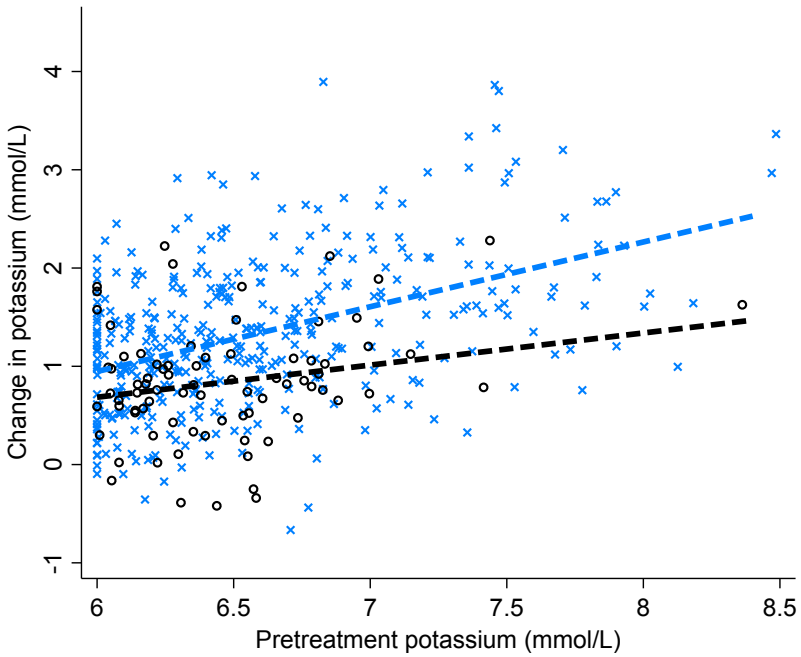
Number of missing pretreatment pH observations imputed = 71 (15%). [1] Percent change in coefficient compared to univariable regression. [2] Percent change in coefficient compared to Model 1 regression. [3] Percent change in coefficient compared to Model 2 regression.

Figure 1. Study flow diagram showing search for eligible patients and exclusions.



*Due to the low number of patients with cirrhosis, the screening for eligible patients between Oct 2016 and Dec 2018 was primarily conducted to identify additional patients with cirrhosis, and the controls were identified only from the period between Jan 2019 and Mar 2020.

Figure 2. Scatterplot and univariate linear regression of the change in blood potassium level in patients with cirrhosis (black circles and line) compared to controls (blue crosses and line), showing that patients with cirrhosis were observed to have a decreased response to potassium lowering with insulin-glucose treatment.



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig.1
		(b) Give reasons for non-participation at each stage	Fig. 1
		(c) Consider use of a flow diagram	Fig. 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table footnotes
		(c) Summarise follow-up time (eg, average and total amount)	standard
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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An Observational Study of the Relative Efficacy of Insulin-glucose Treatment for Hyperkalaemia in Patients with Liver Cirrhosis

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Title Page

Title:

An Observational Study of the Relative Efficacy of Insulin-glucose Treatment for Hyperkalaemia in Patients with Liver Cirrhosis

Running title:

Insulin-glucose treatment and cirrhosis

Authors:

Andy K.H. Lim [1,2,3]

Ljiljana Crnobrnja [1]

Manogna Metlapalli [1]

Cathy Jiang [1]

Rene Wang [1]

Jeanette H. Pham [1]

Joshua H. Abasszade [1]

Affiliations:

[1] General Medicine, Monash Health, Clayton, Victoria 3168, Australia.

[2] Nephrology, Monash Health, Clayton, Victoria 3168, Australia.

[3] Department of Medicine, School of Clinical Sciences, Monash University, Clayton, Victoria 3168, Australia.

Corresponding author:

A/Professor Andy Lim

MBBS FRACP MMed(ClinEpi) PhD

Department of General Medicine and Nephrology

Monash Health

246 Clayton Road, Clayton, VIC 3168, Australia

E: andy.lim@monash.edu

T: +61 3 9544 8736

Abstract

Objectives: To determine if liver cirrhosis is associated with reduced efficacy of insulin-glucose treatment in moderate to severe hyperkalaemia.

Design: Retrospective, cohort study.

Setting: Two secondary and one tertiary care hospital at a large metropolitan healthcare network in Melbourne, Australia.

Participants: This study included 463 adults with a mean age of 68.7 ± 15.8 years, comprising 79 patients with cirrhosis and 384 without cirrhosis as controls, who received standard insulin-glucose treatment for a serum potassium ≥6.0 mmol/L from Oct 2016 to Mar 2020. Patients were excluded if they received an insulin infusion, or if there was inadequate follow-up data for at least 6 hours after IDT due to death, loss to follow up, or inadequate biochemistry monitoring. The mean Model for End-stage Liver Disease (MELD) score in patients with cirrhosis was 22.2 ± 7.5, and the distribution of the Child-Pugh score for cirrhosis was: Class A (24%), B (46%), C (30%).

Outcome measures: The primary outcome was the degree of potassium lowering and the secondary outcome was the proportion of patients who achieved normokalaemia, within 6 hours of treatment.

Results: The mean pretreatment potassium for the cohort was 6.57 ± 0.52 mmol/L. After insulin-glucose treatment, mean potassium lowering was 0.84 ± 0.58 mmol/L in patients with cirrhosis compared to 1.33 ± 0.75 mmol/L for controls (p<0.001). The proportion of patients achieving normokalaemia was 33% for patients with cirrhosis, compared to 53% for controls (p=0.001). By multivariable regression, on average, liver cirrhosis was associated with a reduced potassium lowering effect of 0.42 mmol/L (95% CI: 0.22 to 0.63 mmol/L, p<0.001) from insulin-glucose treatment, after adjusting for age, serum creatinine, cancer, pretreatment potassium level, β-blocker use, and cotreatments (sodium polystyrene sulfonate, salbutamol, sodium bicarbonate).

Conclusions: Our observational data suggests reduced efficacy of insulin-glucose treatment for hyperkalaemia in patients with cirrhosis.

Strengths and limitations of this study

- To our knowledge, this is the first study to demonstrate an association between liver cirrhosis and a reduced response to insulin-glucose treatment in hyperkalaemia management in a real-world clinical cohort.
- We used multivariable modelling to account for potential confounding due to age, comorbidities, and concurrent treatments for hyperkalaemia.
- It was a retrospective observational study, and some residual confounding and other treatment biases may not have been fully accounted for.
- Due to the high frequency of cotreatments for hyperkalaemia, the overall potassium lowering effect of insulin-glucose treatment could be overestimated, so we used our most conservative estimate for inference.

Keywords

Hyperkalemia, potassium, insulin-glucose, insulin-dextrose, cirrhosis, chronic liver disease, efficacy

Word Count

Main text 3581 words, abstract 298 words.

INTRODUCTION

Hyperkalemia is an elevated blood potassium (K^+) level which is associated with the risk of heart rhythm instability that can be fatal. Intravenous insulin-glucose (also known as insulin-dextrose) treatment rapidly lowers blood K^+ by shifting K^+ intracellularly through an indirect effect of activating the cell membrane sodium-K^+ ATPase which then promotes cellular influx of K^+ in exchange for sodium. Insulin-glucose is the preferred treatment for hyperkalemia in the acute setting as methods which enhance K^+ elimination with oral cation exchange resins such as sodium polystyrene sulfonate require many hours or days to be effective. A typical insulin-glucose treatment involves 10 units of regular insulin given intravenously with 25 g of glucose (as intravenous 50 mL of 50% glucose or 50% dextrose).

The efficacy of insulin-glucose shows wide variance such that meta-analysis and pooling of treatment effect has not been possible to date.[1 2] Some of the heterogeneity in reported insulin-glucose efficacy may be due to variations in the study populations and insulin dosing. However, our recent work suggested that specific patient factors may also contribute to this heterogeneity and there was a suggestion that patients with liver cirrhosis may have a modified response to insulin-glucose treatment.[3] Furthermore, there are experimental and observational data showing that patients with liver fibrosis and cirrhosis have insulin resistance, which has an effect on glucose metabolism.[4-6] However, it not clear that K^+ metabolism is altered in patients with cirrhosis, but it is a plausible hypothesis that insulin-glucose may not be as efficacious in patients with cirrhosis compared to patients without cirrhosis in the management of hyperkalaemia.

Hyperkalaemia is a frequent observation in hospitalized patients with cirrhosis, with an estimated prevalence of 12% to 14%.[7] Several observational studies have also found an association between hyperkalaemia and a poorer prognosis and mortality in patients with cirrhosis.[7-9] Thus, it would be important to determine if an established treatment for hyperkalaemia may be compromised in patients with cirrhosis. The aim of this study was to specifically determine if cirrhosis affects the efficacy of insulin-glucose treatment by comparing the K^+ lowering effect of insulin-glucose in patients with and without cirrhosis.

METHODS

Study design and setting

This was a retrospective cohort study of patients who received insulin-glucose treatment at any location (emergency department, inpatient ward, intensive care unit) between Oct 2016 and

Mar 2020, within three major Melbourne metropolitan hospitals (two secondary care and one tertiary care) in a large healthcare network in the state of Victoria, Australia. The healthcare network is the largest public health service in the state, providing healthcare to around one quarter of the population of Melbourne and handling over 260,000 hospital admissions annually.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this study.

Study participants

Only adult patients (≥18 years) with a serum K^+ ≥6.0 mmol/L who received treatment with standard insulin-glucose (intravenous bolus of 10 units of regular insulin with 25 grams of glucose as 50% glucose) were eligible for the study. We used the International Statistical Classification of Diseases and Related Health Problems Tenth Revision (ICD-10) coding to screen for patients with hyperkalaemia. The K^+ levels and insulin-glucose treatment were confirmed by a systematic review of the biochemistry results and medication charts. Assignment to the cirrhosis group is based on an established history of cirrhosis (none of the cases were new diagnoses) and clinical complications of portal hypertension such as encephalopathy, ascites, splenomegaly or varices, or patients with a clear radiological evidence of cirrhosis. Patients with abnormal liver function without clinical or radiological evidence of cirrhosis remained in the control group.

Insulin-glucose treatment

All study sites used a standard protocol for insulin-glucose treatment as part of an established healthcare network policy and procedure document endorsed by the Medication Safety and Therapeutics Committee and Chief Medical Officer. Medical supplies for all sites were also centrally managed across the network hospitals so there was no variation in materials used. Briefly, 10 units (0.1 mL) of short-acting insulin is drawn into an insulin syringe and added to a 50 mL glass vial of 50% glucose (0.2 units/mL) and mixed well by repeated inversion. The mixed contents are drawn into a standard 50 mL polypropylene syringe and immediately administered via a syringe driver over 15 to 30 minutes. The use of a standard protocol, polypropylene syringes and identical materials avoids significant variations in intravenous insulin delivery which may be observed when different materials or infusion times are used.[10]

Exclusions

Patients were excluded from the study if they received a continuous insulin and/or glucose infusion instead of the standard insulin-glucose protocol, or if there was inadequate follow-up data for at least 6 hours after treatment due to death, loss to follow up, or inadequate K^+ monitoring. Adequate K^+ monitoring was defined as the availability of ≥2 posttreatment biochemistry tests to determine K^+ levels, with the first posttreatment test being performed within 2 hours of the completion of the insulin-glucose infusion, and the last within 6 hours of treatment. The lowest K^+ of any test is taken as the trough level.

Ethics approval and patient consent

This study was approved by the Monash Health Human Research Ethics Committee (Monash HREC reference: RES-20-0000-604Q-67939). The ethics committee waived individual patient consent due to the retrospective and observational nature of the study, which used data collected during routine care based on existing treatment protocols. No additional information was sought from patients beyond existing documentation and available laboratory results.

Study outcomes

For the primary outcome, we estimated the change in K^+ (ΔK^+) as the pretreatment K^+ *minus* the posttreatment K^+, thus a negative ΔK^+ value represents the amount of K^+ lowering. The secondary outcome measure was the proportion of patients who achieved normokalaemia (defined as a K^+<5.4 mmol/L) within 6 hours of insulin-glucose treatment, which is the period of protocol monitoring.

Variable definitions

Acute kidney injury (AKI) was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) clinical criteria.[11] Chronic kidney disease (CKD) was defined as a baseline estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 using the CKD-EPI equation, and using a strategy suggested by Siew et al to determine baseline kidney function.[12] We determined the presence of sepsis using the definitions recommended by the Sepsis-3 guidelines.[13] Obesity was defined as a body mass index (BMI) ≥30 kg/m^2 calculated from either measured or self-reported body weight and height. We used the Malnutrition Universal Screening Tool (MUST)[14] score of ≥2 points to define a high risk of malnutrition. Patients were deemed to have active cancer if they had a locally invasive or metastatic solid cancers, or haematological cancer which required chemotherapy, hormonal therapy or immune therapy.

This definition excluded patients with a remote history of cancer and patients with cancer who were in remission and no longer receiving active treatment. We report the Model for End-Stage Liver Disease incorporating serum sodium (MELD-sodium) score[15] and the Child-Pugh score[16] as markers for the severity of liver disease for patients with cirrhosis. Hypoglycaemia was defined as a blood glucose <3.9 mmol/L (70 mg/dL) per American Diabetes Association recommendation.[17]

Statistical analysis

To examine the association between categorical variables, we used the chi-squared (χ^2) statistic. We used the *t*-test to compare the means of continuous variables between the cirrhosis and control groups, or ANOVA for multigroup comparisons, and the Wilcoxon rank sum test to compare nonparametric distributions. Multivariable linear regression was used to model the association between the ΔK^+ and cirrhosis status. In the initial multivariable model, we included the main epidemiological factor of cirrhosis, potential confounders, variables with a univariable $p<0.10$, and variables with significant pretreatment differences between the cirrhosis and control groups. Through backwards elimination, we progressed to the final multivariable model and retained cotreatment medications, variables with a $p<0.05$ or variables which changed the *b* coefficient for cirrhosis by more than 10%. Statistical interactions between relevant variables were assessed at a 1% level of significance. Multicollinearity was assessed by examining the variance inflation factor. In the final model, multiple imputation was performed for the missing pretreatment blood pH observations, using a linear regression imputation method with 50 imputed datasets. The variables used in the imputation model were age, pretreatment pH, urea, creatinine, bicarbonate (HCO_3^-), K^+, cirrhosis, CKD, cancer, and β-blocker use. Sensitivity analysis was performed by excluding patients who received a second insulin-glucose treatment within the 6-hour monitoring period. When comparing multivariable models and for the sensitivity analysis, we considered a change in the *b* coefficient for cirrhosis of 10% or more as significant. Finally, residual and leverage plots were used to identify outliers and influential observations and the linearity of the continuous independent variables was examined using fractional polynomials. All analyses were performed with STATA version 16 (StataCorp, TX, USA). A $p<0.05$ was considered statistically significant.

RESULTS

Baseline patient characteristics

A total of 79 patients with cirrhosis and 384 patients without cirrhosis (controls) were included in the study (Figure 1). Patients were mostly older (mean age, 69 years) and there was a 2:1 ratio of males to females in the study. Kidney disease was prevalent, with 69% of all patients demonstrating baseline CKD, and 51% of patients suffering from AKI. By comparing patients based on cirrhosis status, both groups were well matched for hospital length of stay, intensive care unit length of stay, requirement for ventilation, rate of AKI and sepsis, diabetes, BMI, malnutrition risk, and active cancer (Table 1). On the other hand, patients with cirrhosis were on average 4.8 years younger than controls, had a lower admission serum creatinine and a smaller proportion with CKD. Patients with cirrhosis were also more likely to be treated with non-selective β-blockers, furosemide, spironolactone, and trimethoprim-sulfamethoxazole, when compared to controls (Table 1).

Patients with cirrhosis

Of the 79 patients with cirrhosis, the most frequent implicated aetiologies of cirrhosis (non-mutually exclusive) were alcoholic hepatitis (39 of 79 patients, 49.4%), non-alcoholic fatty liver disease (20 of 79 patients, 25.3%), and chronic viral hepatitis (19 of 79 patients, 24.1%). The less frequent aetiologies (<5%) included drug-induced liver disease, autoimmune hepatitis, cardiac cirrhosis, sclerosing cholangitis and cryptogenic cirrhosis. In terms of the severity of the chronic liver disease, the relative frequency distribution of the Child-Pugh staging of cirrhosis were: Grade A (24.0%), Grade B (45.6%), and Grade C (30.4%). The mean ± standard deviation (SD) of the MELD-sodium score was 22.2 ± 7.5, and the MELD-sodium scores showed a normal distribution. None of the patients with cirrhosis underwent liver transplantation during their index admission.

Biochemistry and cotreatments

The mean ± SD of the pretreatment K^+ levels for the entire cohort was 6.57 ± 0.52 mmol/L. There was a small difference in the mean pretreatment K^+ of 0.13 mmol/L between patients with cirrhosis and controls, which is of uncertain clinical significance. There was also a small difference in mean blood pH of 0.02 which is of uncertain clinical significance, even though serum bicarbonate levels were not different (Table 2). Overall, the mean ΔK^+ was −1.24 mmol/L after insulin-glucose treatment. However, patients with cirrhosis had a smaller ΔK^+ compared to control patients (Table 2 and Figure 2A), despite no significant differences in the ΔpH and ΔHCO_3^- levels. Furthermore, the proportion of patients who achieved normokalemia was smaller in patients with cirrhosis compared to control patients (Table 2).

In terms of cotreatments, patients with cirrhosis were more likely to receive treatment with sodium polystyrene sulfonate and at higher doses compared to controls. There was also weak evidence that patients with cirrhosis were more likely to receive a repeat insulin-glucose treatment but less likely to receive sodium bicarbonate (Table 2). Treatment with nebulised salbutamol for hyperkalaemia was observed in 12.6% of patients, with no appreciable difference between the groups. Concurrent administration of intravenous furosemide occurred in 7.6% of patients, equally distributed between controls and patients with cirrhosis (Table 2), but the clinical response to furosemide could not be determined as urine output was not systematically measured or documented.

Regression of ΔK^+

In the univariable analysis, the *b* coefficient for the regression of ΔK^+ on cirrhosis status was −0.49 (95% CI: −0.67 to −0.32, $p<0.001$). The results of the univariable regression analysis of ΔK^+ on covariates are summarised in Table 3. Creatinine values were log transformed prior to analysis. In the multivariable models, we included the variables which were associated with ΔK^+ or variables which were significantly different in patients with cirrhosis compared to controls. Variables which were not statistically significant or did not show a significant confounding effect were dropped from the model. The result of the multivariable regression is summarised in Table 4 and visually represented in Figure 2B.

After allowing for age, creatinine, cancer, pretreatment K^+, β-blockers, and cotreatments, the adjusted *b* coefficient for the linear regression of ΔK^+ on cirrhosis status was −0.48 (95% CI: −0.64 to −0.31, $p<0.001$). This was associated with a standardized coefficient (β) for cirrhosis of −0.24. There was a large overall effect size for the model ($\eta^2=0.30$) and the effect size for cirrhosis was considered moderate (partial $\eta^2=0.07$). On average, the effect of insulin-glucose on ΔK^+ increased with higher pretreatment K^+ levels ($b=0.65$, 95% CI: 0.53 to 0.78, $p<0.001$) as noted in Figure 2B, but there was no significant interaction between cirrhosis and pretreatment K^+ (p for interaction=0.12).

We also conducted sensitivity analyses by excluding patients who received a second insulin-glucose treatment within 6 hours of the initial treatment (Table 4). There was a 9% to 12% change in the *b* coefficient for cirrhosis depending on whether blood pH was included in the model. The most conservative *b* estimate of −0.42 (95% CI: −0.61 to −0.23) was accepted for inference.

Glycaemia

Prior to insulin-glucose treatment, the mean baseline glucose for the entire cohort was 10.7 mmol/L, which reflected the high prevalence of diabetes in this population of patients with hyperkalaemia (Table 2). However, baseline glucose was not as high in patients with cirrhosis compared to controls (mean difference 3.2 mmol/L, 95% CI: 2.0-4.5 mmol/L). Posttreatment trough glucose was similar in both groups but the change in glucose from baseline was significantly smaller in patients with cirrhosis compared to controls (mean difference 4.0 mmol/L, 95% CI: 3.0-5.0 mmol/L). The incidence of hypoglycaemia after insulin-glucose treatment was 18.8%, and there was weak evidence that patients with cirrhosis had a 50% lower odds of hypoglycaemia compared to controls (p=0.07).

Cirrhosis stage and timing of posttreatment K^+ test

To determine if insulin resistance was incremental with the severity of liver disease, we examined if there was an association between ΔK^+ and surrogate markers of liver disease severity. We found no association between ΔK^+ and either the MELD score (Figure 3A) or Child-Pugh stage (Figure 3B). The differences in mean ΔK^+ between the Child-Pugh categories were not statistically significant by ANOVA (p=0.57) and there was also no evidence of a linear trend across the categories (p=0.29).

To determine if the trough K^+ levels were biased by the timing of posttreatment laboratory testing, we examined the distribution of testing times between the control patients and patients with cirrhosis. Firstly, the distribution of testing times appear nearly identical graphically (Figure 3C). Secondly, a non-parametric test for the equality of distributions showed no significant difference in the distribution of testing times (p=0.61). The median (IQR) testing times for controls compared to patients with cirrhosis were 125 min (60-206 min) and 119 min (61-200 min), respectively.

DISCUSSION

In this observational study, we sought to determine the real-world clinical significance of insulin resistance in the context of the therapeutic action of insulin in hyperkalemia management. The main finding was that patients with cirrhosis had a decreased response to K^+ lowering by insulin-glucose treatment compared to patients without cirrhosis. We estimated that the magnitude of the difference was 0.48 mmol/L, on average, after adjusting for age, creatinine, cancer, pretreatment K^+, β-blocker treatment, and cotreatments. The magnitude of the difference was maintained even after allowing for the pretreatment blood pH and HCO_3^-

levels or allowing for the ΔpH and ΔHCO_3^- levels. However, a more conservative estimate of this difference was 0.42 mmol/L, derived from sensitivity analysis after excluding patients who received a second insulin-glucose treatment. To our knowledge, this is the first study to demonstrate a reduced efficacy of insulin-glucose treatment for hyperkalemia in patients with established cirrhosis.

Compared to controls, patient with cirrhosis in our study demonstrated a smaller change in blood glucose following insulin-glucose treatment, and experienced less hypoglycaemia. Our findings support previous observational and experimental human studies that insulin resistance and hyperinsulinaemia is common in patients with cirrhosis.[4 18 19 20] Insulin can function to shift both glucose and K^+ into cells, the former through promoting GLUT-4 translocation to the cell membrane in muscle and adipose tissue, and the latter via stimulation of the cell membrane sodium-H^+ antiporter thereby promoting activation of the sodium-K^+ ATPase. However, there is much debate whether glucose and K^+ metabolism can be differentially regulated in the setting of insulin resistance. Observational data suggests that patients with type 2 diabetes and insulin resistance have a higher serum K^+ than patients without insulin resistance.[21] However, experimental data indicates that the effect of insulin on glucose and K^+ can be dissociated.[22 23] Hepatic uptake of K^+ accounts for a significant proportion of K^+ lowering after an insulin infusion but even cirrhotic livers may retain this function as demonstrated in an in vivo transplantation study.[24] Another speculative hypothesis involves possible alterations in the expression and activity of the sodium-K^+ ATPase in hyperinsulinaemia and insulin-resistant states.[25] Alternatively, some other post-receptor alterations may be contributory in modifying the insulin action on target cells in cirrhosis.[20]

Although the mechanistic explanation for our observation is unclear, others have shown that patients with cirrhosis have a higher serum K^+ in response to oral K^+ loading despite insulin hypersecretion, which was not observed in healthy controls, and in the setting of an equivalent renal K^+ excretion in both groups.[26] Furthermore, we do not believe that the observed difference in K^+ lowering with insulin-glucose treatment can be explained by differences in the acid-base status between the two groups. Neither a drop in blood pH nor serum HCO_3^- were observed in the patients with cirrhosis. Furthermore, both the ΔpH and ΔHCO_3^- were not significantly different between the two groups. Even though the statistical effect size of cirrhosis status on ΔK^+ was only moderate in the regression model, the clinical significance of the reduced response to insulin-glucose in patients with cirrhosis was evident by the lower proportion of patients with cirrhosis who achieve normokalaemia compared to controls.

Our findings may be generalized to any adult patient who receives a standard insulin-glucose treatment for hyperkalaemia but may not be valid for patients receiving continuous insulin infusions or other variations in insulin dosing as these patients were explicitly excluded from our study. Most patients with cirrhosis in our study had Child-Pugh B or C cirrhosis and a high MELD-sodium score. Thus, we suggest that the finding of a reduced efficacy of insulin-glucose in lowering K^+ only applies to patients with a clear diagnosis of cirrhosis, particularly those with more advanced cirrhosis.

Study strengths and limitations

To our knowledge, this is the first study to demonstrate an association between liver cirrhosis and a reduced response to insulin-glucose treatment in hyperkalaemia management in a real-world clinical cohort. Another strength is the use of multivariable modelling to account for potential confounding due to age, comorbidities, and concurrent treatments for hyperkalaemia. However, this was a retrospective observational study, and some residual confounding and other treatment biases may not have been fully accounted for. There was a small possibility that we may have failed to identify some eligible patients by using ICD-10 coding for hyperkalaemia. However, as diagnosis coding determines healthcare funding, the number of missed cases was likely to be negligible. Due to the high frequency of cotreatments for hyperkalaemia, the overall potassium lowering effect of insulin-glucose treatment could be overestimated. Even though the distribution of K^+ testing times after treatment was similar in both groups, the lack of standardised times may be a source of bias due to the dynamic nature of the response to insulin-glucose treatment. We may have also underestimated the absolute K^+ lowering effect of insulin-glucose if testing did not coincide with the actual physiological trough. However, as testing times were not significantly different in the two groups, it is unlikely that the relative differences in K^+ lowering between controls and patients with cirrhosis was significantly biased by testing time. Finally, we did not determine if the observed differences in K^+ lowering was associated with any 'hard' adverse outcomes such as arrhythmias or death.

Conclusions

The efficacy of K^+ lowering with insulin-glucose treatment is reduced in patients with cirrhosis when the serum K^+ is 6.0 mmol/L or higher. Therefore, a greater consideration for adjunct treatments for K^+ lowering may be justified in patients with cirrhosis.

Suggestions for further research

A prospective study incorporating an assessment of the degree of insulin resistance (and possibly matching patients with cirrhosis and controls on this variable) and unbiased by cotreatments would provide stronger evidence for a reduced efficacy of insulin-glucose treatment in hyperkalaemia treatment for patients with cirrhosis. An interventional study using different insulin doses may also be useful for finding the insulin dose for patients with cirrhosis which provides the equivalent K^+ lowering effect observed in patients without cirrhosis. Finally, we could not demonstrate an association between the efficacy of insulin-glucose treatment and the MELD and Child-Pugh scores in patients with cirrhosis. Future studies could consider other methods or biomarkers to determine the exact relationship between the severity of liver disease and the dose-response of insulin-glucose treatment.

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Competing interests

The authors have no conflict of interests to declare.

Author contributions

A.K.H.L. conceptualized and designed the study. L.C, M.M., C.J., R.W, J.H.P., and J.H.A. reviewed and modified the protocol, and performed data collection. A.K.H.L. performed the analysis and drafted the manuscript. All authors contributed to the review and editing of the final version.

Data sharing statement

The data presented in this study may be available on reasonable request from the corresponding author, subject to approval by the health service research directorate.

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Table 1. Baseline characteristics of patients before insulin-glucose treatment

Characteristic	All patients N = 463	No cirrhosis n = 384	Cirrhosis n = 79	*p*-value
Age, mean (SD), years	68.7 (15.8)	69.5 (16.2)	64.7 (13.0)	0.005
Female, n (%)	172 (37.2)	145 (37.8)	27 (34.2)	0.55
Hospital length of stay, median (IQR), days	7 (3-14)	6 (3-13)	7 (2-17)	0.47
ICU admission, n (%)	135 (29.2)	110 (28.7)	25 (31.7)	0.59
ICU length of stay, median (IQR), hours [1]	69 (40-164)	65 (39-134)	96 (62-176)	0.29
Ventilated, n (%)	69 (14.9)	55 (14.3)	14 (17.7)	0.44
Duration of ventilation, median (IQR), hours [2]	40 (18-134)	37 (15-128)	100 (74-140)	0.12
Admission urea, median (IQR), mmol/L	19 (13-27)	20 (13-27)	19 (14-28)	0.99
Admission creatinine, median (IQR), µmol/L	224 (142-482)	250 (145-537)	189 (132-296)	0.001
Chronic kidney disease, n (%)	318 (68.7)	275 (71.6)	43 (54.4)	0.003
Acute kidney injury, n (%)	238 (51.4)	191 (49.7)	47 (59.5)	0.12
Stage 1	103 (22.3)	82 (21.4)	21 (26.5)	0.46 [3]
Stage 2	74 (16.0)	60 (15.6)	14 (17.7)	
Stage 3	61 (13.2)	49 (12.8)	12 (15.2)	
Sepsis, n (%)	59 (12.7)	46 (12.0)	13 (16.5)	0.28
Body mass index, mean (SD), kg/m^2	28.4 (7.9)	28.3 (7.9)	28.8 (8.2)	0.62
Obese, n (%)	154 (33.6)	129 (34.0)	25 (31.7)	0.69
High malnutrition risk, n (%)	82 (17.7)	65 (16.9)	17 (21.5)	0.33
Diabetes mellitus, n (%)	273 (59.0)	229 (59.6)	44 (55.7)	0.52
Active cancer, n (%)	77 (16.6)	63 (16.4)	14 (17.7)	0.78
Beta-blockers, n (%)				
β1-selective	168 (36.3)	149 (38.8)	19 (24.1)	<0.001
Non-selective	17 (3.7)	6 (1.6)	11 (13.9)	
ACE inhibitor or ARB, n (%)	157 (33.9)	135 (35.2)	22 (27.9)	0.22
Furosemide, n (%) [4]				
Low dose (20 mg to 80 mg daily)	126 (27.2)	88 (22.9)	38 (48.1)	<0.001
High dose (100 mg to 500 mg daily)	48 (10.4)	38 (9.9)	10 (12.7)	
Spironolactone, n (%)				
Low dose (12.5 mg to 50 mg daily)	68 (14.7)	41 (10.7)	27 (34.2)	<0.001
High dose (75 mg to 200 mg daily)	24 (5.2)	1 (0.3)	23 (29.1)	
Trimethoprim-sulfamethoxazole, n (%)	39 (8.4)	26 (6.8)	13 (16.5)	0.005
History of hyperkalaemia, n (%)	56 (12.1)	46 (12.0)	10 (12.7)	0.87
Sodium polystyrene sulfonate, n (%) [4]	10 (2.2)	9 (2.4)	1 (1.3)	0.55
Subcutaneous insulin, n (%)	114 (24.6)	93 (24.2)	21 (26.6)	0.66
Metformin, n (%)	67 (14.5)	58 (15.0)	9 (11.4)	0.40
Other oral hypoglycemic agents, n (%)				
Sulfonylurea	39 (8.4)	36 (9.4)	3 (3.8)	0.20
Sulfonylurea + gliptin	22 (4.8)	20 (5.2)	2 (2.5)	
Gliptin	33 (7.1)	28 (7.3)	5 (6.3)	
Others	10 (2.2)	8 (2.1)	2 (2.5)	

[1] Only for patients admitted to intensive care unit (ICU). [2] Only for patients on ventilation. [3] Categorical data analysis by acute kidney injury stage. [4] Taken as long-term medication and not included in the acute management of hyperkalaemia.

Table 2. Biochemistry and hyperkalemia cotreatments by cirrhosis status

Characteristic	All patients N = 463	No cirrhosis n= 384	Cirrhosis n = 79	*p*-value
Pretreatment K^+, mean (SD), mmol/L	6.57 (0.52)	6.60 (0.54)	6.47 (0.41)	0.041
Pretreatment HCO_3^-, mean (SD), mmol/L	20.7 (5.0)	20.8 (5.0)	20.1 (4.6)	0.22
Pretreatment pH, mean (SD) [1]	7.29 (0.09)	7.29 (0.09)	7.31 (0.09)	0.046
Posttreatment K^+, mean (SD), mmol/L	5.33 (0.70)	5.27 (0.70)	5.63 (0.63)	<0.001
Posttreatment HCO_3^-, mean (SD), mmol/L	20.7 (5.0)	20.8 (5.0)	19.7 (4.7)	0.07
Posttreatment pH, mean (SD) [2]	7.30 (0.09)	7.30 (0.09)	7.32 (0.09)	0.044
Change in K^+, mean (SD), mmol/L	−1.24 (0.74)	−1.33 (0.75)	−0.84 (0.58)	<0.001
Change in HCO_3^-, mean (SD), mmol/L	0.11 (2.11)	0.06 (2.15)	0.34 (1.93)	0.28
Change in pH, mean (SD) [3]	0.01 (0.06)	0.01 (0.06)	0.01 (0.04)	0.87
Normokalemia achieved, n (%)	230 (49.7)	204 (53.1)	26 (32.9)	0.001
Cotreatments:				
Repeat insulin-glucose <6 h, n (%)	93 (20.1)	71 (18.5)	22 (27.9)	0.06
Repeat interval, mean (SD), min [4]	184 (94)	183 (94)	188 (97)	0.86
Sodium polystyrene sulfonate, n (%)	292 (63.0)	234 (60.9)	58 (73.4)	0.036
15 grams	56 (12.1)	47 (12.2)	9 (11.4)	
30 to 60 grams	236 (51.0)	187 (48.7)	49 (62.0)	
Salbutamol, n (%)	57 (12.3)	50 (13.0)	7 (8.9)	0.31
5 mg	36 (7.8)	32 (8.3)	4 (5.1)	
10-20 mg	21 (4.5)	18 (4.7)	3 (3.8)	
Sodium bicarbonate, n (%)	47 (10.1)	42 (10.9)	5 (6.3)	0.07
<100 mmol	23 (5.0)	18 (4.7)	5 (6.3)	
≥100 mmol	24 (5.2)	24 (6.3)	0 (0)	
IV furosemide, n (%)	35 (7.6)	28 (7.3)	7 (8.9)	0.69
20 to 40 mg	25 (5.4)	20 (5.2)	5 (6.3)	
80 to 200 mg	10 (2.2)	8 (2.1)	2 (2.5)	
Glycaemia:				
Pretreatment glucose, mean (SD), mmol/L	10.7 (5.3)	11.3 (5.4)	8.1 (3.8)	<0.001
Trough glucose, mean (SD), mmol/L	7.2 (4.1)	7.0 (4.0)	7.8 (4.4)	0.12
Change in glucose, mean (SD), mmol/L	−3.6 (4.3)	−4.3 (4.0)	−0.3 (4.0)	<0.001
Hypoglycaemia, n (%)	87 (18.8)	78 (20.3)	9 (11.4)	0.07

[1] missing observations = 69 (14.9%).
[2] missing observations = 42 (9.1%).
[3] missing observations = 78 (16.8%).
[4] patients who received a second insulin-glucose treatment only.

Table 3. Univariable linear regression

Variable	*b*	(95% CI)	*p*-value
Cirrhosis	−0.49	(−0.67 to −0.32)	<0.001
Age, per 10 years	−0.05	(−0.09 to −0.01)	0.029
Female sex	0.02	(−0.12 to 0.16)	0.78
Diabetes	−0.02	(−0.15 to 0.12)	0.83
Insulin-requiring diabetes	−0.05	(−0.21 to 0.11)	0.52
Body mass index, per 5 kg/m^2	−0.02	(−0.07 to 0.02)	0.27
Chronic kidney disease	−0.08	(−0.23 to 0.06)	0.27
Active cancer	−0.14	(−0.33 to 0.04)	0.12
High malnutrition risk [1]	0.14	(−0.04 to 0.31)	0.13
Sepsis	−0.09	(−0.29 to 0.11)	0.38
Creatinine, per log increase	0.02	(−0.01 to 0.04)	0.17
Acute kidney injury	0.00	(−0.14 to 0.13)	0.97
Beta-blockers			
Cardioselective	0.10	(−0.05 to 0.24)	0.41
Non-selective	0.04	(−0.32 to 0.41)	
Pretreatment K^+	0.62	(0.50 to 0.74)	<0.001
Pretreatment HCO_3^-	0.01	(−0.01 to 0.02)	0.31
Pretreatment pH	0.02	(−0.86 to 0.82)	0.96
Repeat insulin-glucose	−0.08	(−0.25 to 0.09)	0.38
Sodium polystyrene sulfonate	−0.22	(−0.36 to −0.08)	0.002
Salbutamol	0.26	(0.05 to 0.47)	0.021
5 mg	0.14	(−0.11 to 0.40)	
10-20 mg	0.42	(0.09 to 0.74)	
Sodium bicarbonate			
<100 mmol	−0.10	(−0.40 to 0.21)	0.002
≥100 mmol	0.55	(0.24 to 0.85)	
Intravenous furosemide	−0.12	(−0.37 to 0.14)	0.37

[1] Malnutrition Universal Screening Tool (MUST) score ≥2.

Table 4. Coefficient for cirrhosis under different multiple regression models

Model	Cirrhosis *b* (95% CI)	Δ *b*
Univariable regression on cirrhosis	−0.49 (−0.67 to −0.32)	
Model 1: Adjusted for age, pretreatment K^+, log creatinine, active cancer, beta-blocker use, and cotreatments (*n*=463) [4]	−0.48 (−0.64 to −0.31)	+2.8% [1]
Model 2: Adjusted for Model 1 covariates and the pretreatment pH levels (*n*=463) [5]	−0.48 (−0.64 to −0.32)	−0.3% [2]
Model 3: Sensitivity analysis, Model 1 covariates excluding patients who received repeat insulin-glucose treatment (*n*=370)	−0.42 (−0.61 to −0.23)	+12.1% [2]
Model 4: Sensitivity analysis, Model 2 covariates excluding patients who received repeat insulin-glucose treatment (*n*=370)	−0.44 (−0.63 to −0.25)	+8.8% [3]

[1] Percent change in *b* coefficient compared to univariable regression. [2] Percent change in *b* coefficient compared to Model 1. [3] Percent change in *b* coefficient compared to Model 2. [4] IV furosemide excluded from cotreatment list as it was balanced in both groups and not statistically significant in the model. [5] Number of missing pretreatment pH observations imputed was 69 (14.9%).

FIGURE LEGENDS

Figure 1. Study flow diagram showing search for eligible patients and exclusions.
Footnote: *Due to an excess number of control patients relative to patients with cirrhosis, we did not require data for controls for the period Oct 2016 - Dec 2018, and patients without cirrhosis during this period were not included in the analysis.

Figure 2. (A) Boxplots demonstrating the magnitude of the observed K^+ reduction after insulin-glucose treatment by cirrhosis status. **(B)** Predicted reduction in serum K^+ (with 95% confidence interval bands) with insulin-glucose treatment derived from multivariable linear regression (adjusted for age, cancer, pretreatment K^+, log-creatinine, β-blockers, cotreatments), with age and log-creatinine held at mean values. Patients with cirrhosis are less responsive to insulin-glucose across a range of pretreatment K^+ levels, but treatment response was greater in both groups at higher levels of pretreatment K^+ even after adjusting for cotreatments received.

Figure 3. (A) Adjusted predicted mean K^+ reduction (with 95% confidence intervals) in patients with cirrhosis, showing no significant change in insulin-glucose treatment efficacy with increasing MELD scores. **(B)** Adjusted predicted mean K^+ reduction was also not different between Child-Pugh stages of cirrhosis. **(C)** Graph of kernel density estimates demonstrating the equal distribution of time intervals from the end of insulin-glucose infusion to the determination of K^+ trough levels in patient with cirrhosis compared to controls.

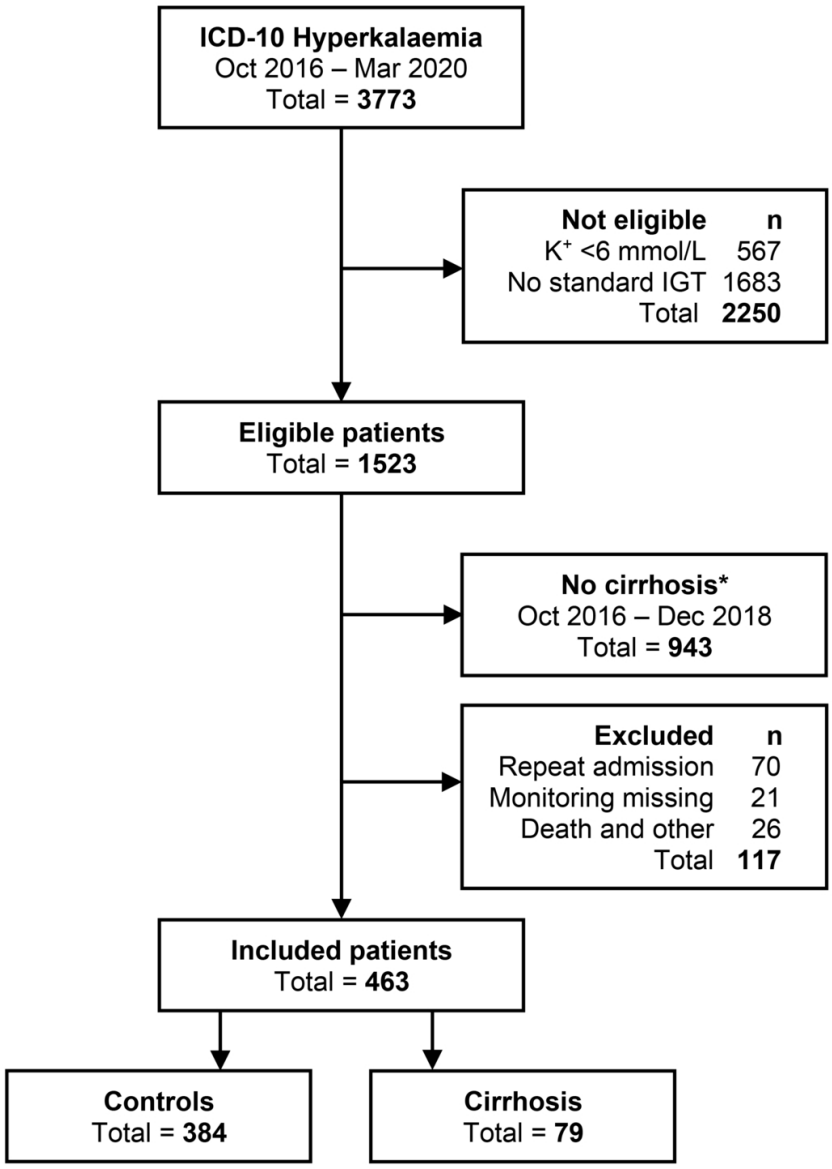

Figure 1. Study flow diagram showing search for eligible patients and exclusions.
Footnote: *Due to an excess number of control patients relative to patients with cirrhosis, we did not require data for controls for the period Oct 2016 - Dec 2018, and patients without cirrhosis during this period were not included in the analysis.

91x125mm (300 x 300 DPI)

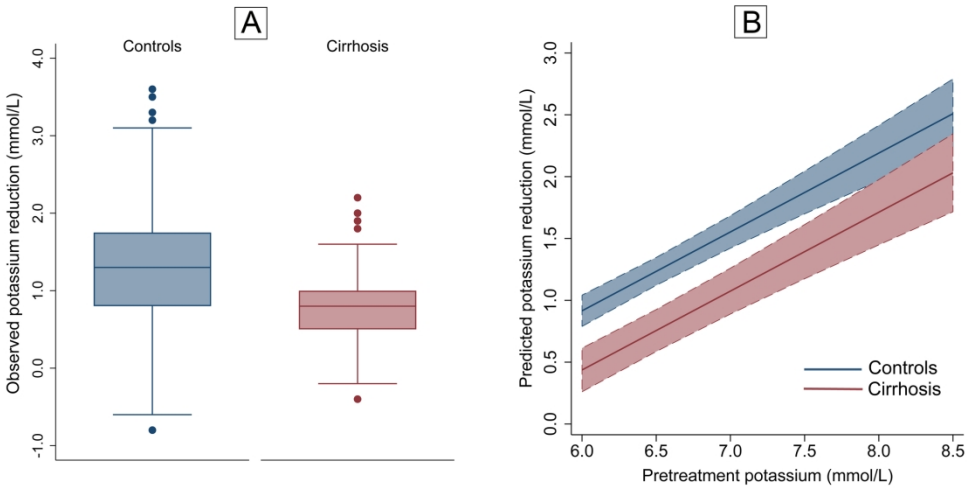

Figure 2. (A) Boxplots demonstrating the magnitude of the observed K+ reduction after insulin-glucose treatment by cirrhosis status. (B) Predicted reduction in serum K+ (with 95% confidence interval bands) with insulin-glucose treatment derived from multivariable linear regression (adjusted for age, cancer, pretreatment K+, log-creatinine, β-blockers, cotreatments), with age and log-creatinine held at mean values. Patients with cirrhosis are less responsive to insulin-glucose across a range of pretreatment K+ levels, but treatment response was greater in both groups at higher levels of pretreatment K+ even after adjusting for cotreatments received.

208x104mm (300 x 300 DPI)

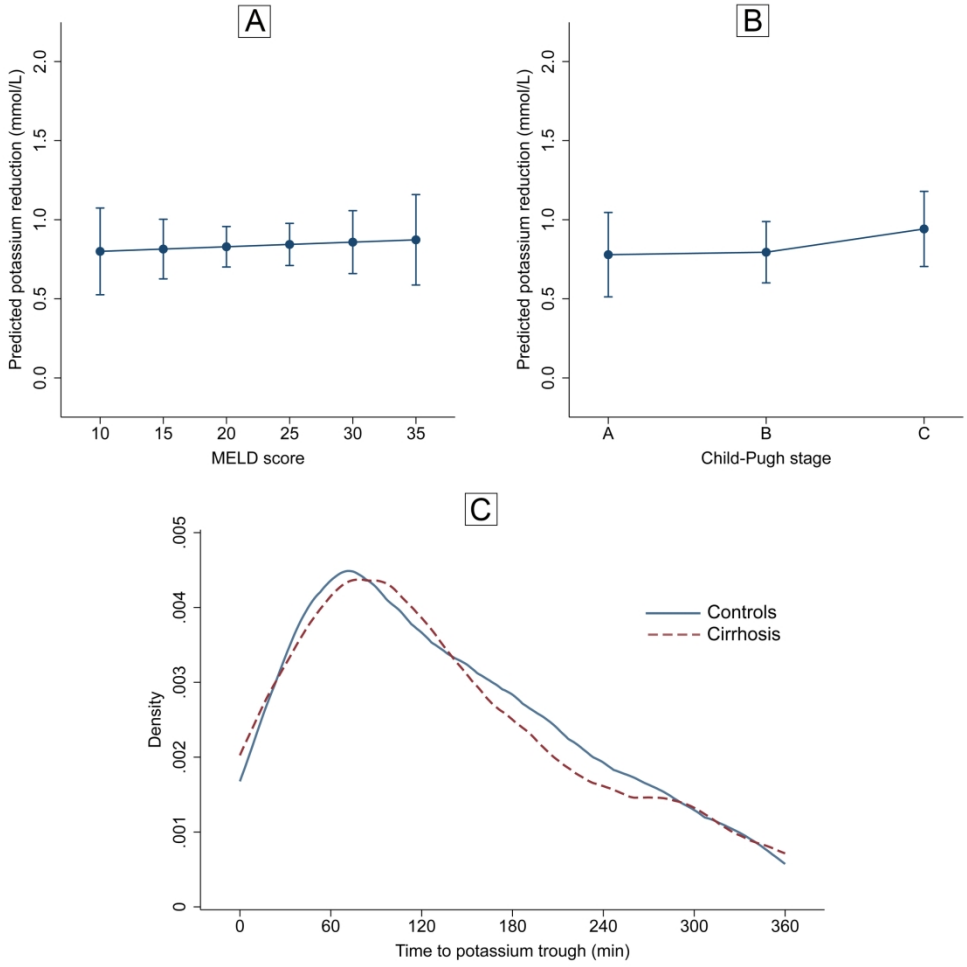

Figure 3. (A) Adjusted predicted mean K+ reduction (with 95% confidence intervals) in patients with cirrhosis, showing no significant change in insulin-glucose treatment efficacy with increasing MELD scores. (B) Adjusted predicted mean K+ reduction was also not different between Child-Pugh stages of cirrhosis. (C) Graph of kernel density estimates demonstrating the equal distribution of time intervals from the end of insulin-glucose infusion to the determination of K+ trough levels in patient with cirrhosis compared to controls.

207x204mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig.1
		(b) Give reasons for non-participation at each stage	Fig. 1
		(c) Consider use of a flow diagram	Fig. 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table footnotes
		(c) Summarise follow-up time (eg, average and total amount)	standard
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.