

BMJ Open Prevalence and factors associated with false hyperkalaemia in Asians in primary care: a cross-sectional study (the Unlysed Hyperkalaemia- the Unseen Burden (UHUB) study)

Alicia Ying Ying Boo ¹, Yi Ling Eileen Koh,² Pei Lin Hu,³ Ngiam Chuan Tan ^{2,4}

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¹Family Medicine, National University Polyclinics, Singapore

²Research, SingHealth Polyclinics, Singapore

³Family Medicine, SingHealth Polyclinics, Singapore

⁴SingHealth-Duke NUS Medical School Academic Clinical Programme, Singapore

Correspondence to

Dr Alicia Ying Ying Boo; alicia_yy_boo@nuhs.edu.sg

ABSTRACT

Serum potassium is part of routine laboratory tests done for patients with hypertension or diabetes mellitus in primary care. Those found to have raised potassium ($K > 5.5$ mmol/L) are recalled for repeat potassium in emergency departments or primary care clinics. Repeat potassium are often normal (≤ 5.5 mmol/L), that is, false hyperkalaemia. Haemolysis is known to cause false hyperkalaemia. We postulated that unlysed false hyperkalaemia was prevalent and was associated with factors such as delayed processing time.

Objective We aimed to determine the prevalence of unlysed false hyperkalaemia and the factors associated with false-and-true-hyperkalaemia.

Setting Outpatients in a cluster of public primary care clinics (polyclinics) in Singapore.

Participants All patients of any ethnicity aged ≥ 21 with serum potassium test done.

Methods Electronic health records of index patients with potassium > 5.5 mmol/L and its corresponding laboratory processing time in seven local polyclinics were reviewed between August 2015 and August 2017. Haemolysed specimens and patients on sodium polystyrene sulfonate (SPS) suspension were excluded. If repeat potassium level was ≤ 5.5 mmol/L within 8 days, the case was defined as false hyperkalaemia. The proportion of such patients was computed to determine its prevalence. Linear and logistic regressions were used to identify the associated factors.

Results The study population comprised of 3014 index cases, of which 1575 had repeat potassium tests without preceding SPS. 86.4% (1362/1575) of them had potassium ≤ 5.5 mmol/L. The average processing time among specimens with potassium ≥ 6.0 mmol/L was 50 min longer, compared with those with potassium < 5.1 mmol/L. Risk factors significantly associated with false hyperkalaemia included estimated glomerular filtration rate (eGFR) (60–89 mL/min/1.73 m², OR=3.25, $p < 0.001$; > 90 mL/min/1.73 m², OR=3.77, $p < 0.001$) and delayed laboratory processing time (beta coefficient 0.001, $p < 0.001$).

Conclusion The prevalence of false hyperkalaemia was 86.4%. Recommendation to repeat potassium tests may target those with eGFR < 60 mL/min/1.73 m².

Strengths and limitations of this study

- The approximate prevalence of false hyperkalaemia (as yet unknown in Singapore and in primary care as a whole) can be discovered.
- Case notes were not reviewed for dietary assessment which could contribute to hyperkalaemia.
- Information on preanalytical variables, such as fist clenching, hyperventilation, ethylenediaminetetraacetic acid (EDTA) contamination and postsplenectomy status, all of which increases the chance of false hyperkalaemia independent of time were not available.
- Patients whose potassium tests were done in emergency departments were unable to be captured.
- Drop-outs may affect the deemed prevalence of false hyperkalaemia, and affect significance of factors which may further predict true hyperkalaemia.

INTRODUCTION

Non-communicable diseases (NCD), such as metabolic and vascular disorders, are rising in prevalence globally.¹ Renal impairment is a major complication among patients with NCD.² Serum electrolytes such as potassium are evaluated as an integral component of renal function assessment. Most of these blood tests are collected in the primary care setting all around the world, where an in-house laboratory (lab) is not available. Instead, these specimens have to be couriered to an off-site lab after blood draw for processing. This will incur a lag time of varying duration before the specimen is processed. One possible outcome of this assessment is elevated serum potassium or hyperkalaemia, which, if true, is potentially lethal as it impacts cardiac muscle function.³ Nonetheless, serum potassium can be artificially raised due to haemolysis, which is a known cause of false hyperkalaemia.⁴

Pseudohyperkalaemia is defined as an elevation of serum potassium while plasma potassium is normal.⁵ There are several other terms which describe the same phenomenon, such as 'spurious hyperkalaemia' or 'factitious hyperkalaemia'.⁶ The literature reports preanalytical factors for pseudohyperkalaemia, which are largely modifiable, such as mechanical lysis, ethylenediaminetetraacetic acid (EDTA) contamination in the tubes, specimen clotting, low temperature,⁷ delayed processing time,⁸ prolonged fist clenching and difficult venipuncture. Patient factors causing hyperkalaemia include hyperventilation, poor renal function (chronic kidney disease (CKD) stage 3A and above) existing haematological diseases, malignancy, postsplenectomy status, treatment with angiotensin-converting enzyme-inhibitors (ACE-i) or with angiotensin receptor blockers (ARB).⁹ A retrospective case-control Japanese study concluded that patients on ACE-i or ARB with a lower body mass index (BMI) are more prone to hyperkalaemia with potassium >5.5 mmol/L.¹⁰ Patients on potassium chloride supplements,¹¹ used for treatment of hypokalaemia, may develop hyperkalaemia if overtreated.

Singapore has a dual public-private primary healthcare system. The official Primary Care Survey in 2014¹² reported that 52% of patients who attended the public primary care clinics or polyclinics were for the treatment of NCD. The local practice guidelines recommend an annual renal function test as part of the health assessment of these patients. Serum potassium is also measured when physicians initiate or titrate the doses of ACE-i or ARB, which are commonly prescribed for these patients.

An unpublished internal audit in a typical local polyclinic showed that false hyperkalaemia (where repeat serum potassium is normal), occurred in 90% of cases where initial serum potassium levels were above 5.0 mmol/L. There are unpublished incident reports where elderly patients treated with usual doses of sodium polystyrene sulfonate (SPS) for 2 days had repeat potassium of 2.4 mmol/L, which is life-threateningly low. This suggests the initial potassium could have been normal to begin with. Consequently, we postulated that false hyperkalaemia was prevalent across the polyclinics and it was associated with modifiable factors.

Plasma potassium is unavailable as a routine test in laboratories within public healthcare institutions to confirm pseudohyperkalaemia. The processing of serum potassium is carried out in an off-site central laboratory, leading to a lag-time before the potassium results are reported. If potassium is raised, local physicians often give a phone call to patients to repeat the serum potassium test for patients' safety. This means that patients have to revisit the clinic doctor and laboratory on a separate occasion, leading to inconvenience and cost. Most patients bear the cost of these repeat consultation and repeat potassium directly, paying either by cash or via their own Medisave, which is a mandatory national healthcare savings scheme, where individuals deposit part of their monthly salary into. Any medication prescribed as part of the management of hyperkalaemia are also paid for by patients or

their family members. This increases healthcare burden, if the initial potassium result turns out to be falsely raised.

Hence, the aim of the study is to determine the prevalence of false hyperkalaemia in a network of polyclinics and to identify the factors associated with false and true hyperkalaemia.

METHODS

Setting and participants

A retrospective study was conducted among all ambulatory patients, in seven public polyclinics situated in central and eastern Singapore between 1 August 2015 and 8 August 2017 inclusive.

Inclusion and exclusion criteria

The study population comprised of ambulatory persons who had their blood sampling done for serum potassium levels at the study sites. All serum potassium tests performed as part of hypertensive and diabetic panels, as well as stand-alone potassium tests, in all patients aged 21 and above, were included. There were no restrictions by diagnosis codes or disease stage.

Data extraction

The data from the electronic medical records were extracted by an independent personnel from the national healthcare information technology vendor (Integrated Health Information Systems), who deidentified the patients to a study identification number (ID). Any potassium done within 8 days of index case inclusive was tagged to the same study ID. Any patients with potassium done after 8 days of index case were given a new study ID number and counted as a separate subject during data extraction.

The following data were extracted:

- (1) Specimen collection time,
- (2) Time processed by central laboratory,
- (3) Polyclinic collected from,
- (4) Age,
- (5) Gender,
- (6) BMI based on most recent body weight and height,
- (7) Potassium levels,
- (8) presence of haemolysis (yes/no),
- (9) Repeat potassium (value and date) within 8 days of first K>5.5 mmol/L inclusive,
- (10) Polyclinic where repeat potassium was collected,
- (11) Creatinine at date of reported hyperkalaemia ($\mu\text{mol/L}$) and within 12 months prior,
- (12) Latest full blood count (FBC) results (within 6 months before and 6 months after first reported K>5.5 mmol/L) and
- (13) Medications prescribed within 6 months prior and 3 months after first hyperkalaemia (filtered). The filtered medications extracted were ACE-i (captopril, enalapril, lisinopril, perindopril, ramipril), ARB (candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan), potassium-sparing diuretics (spironolactone), potassium supplements (potassium chloride tablet, potassium citrate mixture) and the cation-exchange resin, SPS.

The medications extracted included those that potentially caused hyperkalaemia, such as ACE-i, ARB, spironolactone and potassium chloride tablets. Patients

were counted to be on these medications if they were prescribed within 6 months prior to index hyperkalaemia. Six months is the longest refill duration in polyclinics for most patients. Medication that potentially caused hypokalaemia, such as SPS, a cation-exchange resin used to lower serum potassium as treatment for hyperkalaemia¹³ in the outpatient setting, was also extracted for. Patients were counted to be on SPS if it was prescribed between 0 and 2 weeks after index hyperkalaemia.

Definitions

Unlysed specimens with serum potassium >5.5 mmol/L were counted as an index case.¹⁴ A study in an ambulatory setting in the UK in 2006 showed that 25% of the patients with $K>5.8$ mmol/L came back within 6 days of recall to repeat the test.¹⁵ In the local setting, results are usually reviewed with patients within 1 week after blood draw, that is, 8 days inclusive of the day of first blood draw.

Hence, false hyperkalaemia was defined as repeat serum potassium within 8 days of index unlysed hyperkalaemia being ≤ 5.5 mmol, and without any known prescription of SPS during these 8 days. The prevalence of false hyperkalaemia was determined as the percentage of patients whose repeat serum potassium within 8 days of index hyperkalaemia was ≤ 5.5 mmol/L, among all those who repeated serum potassium within 8 days. All these potassium specimens must not be haemolysed. These patients must not be prescribed SPS within those dates.

Processing of collected blood samples

While phlebotomy is carried out within the polyclinics, the biochemical analyses of the blood samples are centralised in an off-site laboratory. Serum potassium specimens are collected at study sites, stored at room temperature, and despatched in a chilled box by couriers coming two times a day. The central laboratory has three potassium analysers which are calibrated daily to ensure their accuracy. Haemolysis is detected by the blood analyser, and confirmed by visual inspection of the blood specimen by laboratory technicians in the central laboratory. The electronic laboratory results are reported back to the polyclinics 3–6 hours later.

A workflow is in place for the central laboratory and clinic to recall via phone, any patient with $K>5.7$ mmol/L (internal threshold value for urgent recall). The urgency of the call is stratified by presence or absence of specimen haemolysis, and the level of serum potassium. These calls usually take place after office hours. Patients are recalled for repeat blood sampling at the polyclinics the next working day if they are asymptomatic, or told to proceed to hospital emergency departments if they are symptomatic or if the potassium value exceeds 6.5 mmol/L.

Data analysis

Deidentified data were analysed using IBM SPSS Statistics for Windows, V.25.0., IBM. If patient had more than two potassium >5.5 mmol/L readings within 8 days of index case, the first would be paired to the second potassium

reading, and the second potassium >5.5 mmol/L would be a new index case, and paired to the third reading, and so on. If two potassium readings are done within an hour, the higher of the two potassium levels were chosen, to depict the 'worst case' scenario. Haemolysed potassium specimens were analysed separately.

Kidney function was measured using estimated glomerular filtration rate (eGFR), which was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula. Time-lag for specimen processing was determined by calculating the difference between the time specimen was processed by central laboratory, and the time blood was drawn from patients at study sites (specimen collection time).

Analysis on subjects with non-haemolysed repeat samples are presented in [tables 1 and 2](#). Descriptive statistics on demographics between two groups (true and false hyperkalaemia) were presented as frequency and percentages. Differences between true and false hyperkalaemia were assessed using Chi-square test and Mann-Whitney U test for categorical and continuous demographic variables, respectively. Significant factors were included in the logistic regression to obtain the adjusted OR of having true hyperkalaemia. Analysis on individual blood samples (not matched to persons' visits) were presented in [table 3](#). Linear regression was done to determine the effect of (1) time lag between collection and processing of serum potassium and (2) haemolysis of samples, on potassium (K) reading. A p value of <0.05 is considered to be statistically significant.

RESULTS

The prevalence of haemolysis was 5.7% among all cases with initial potassium >5.5 mmol/L. Out of those who repeated, 35% (43/123) of the specimens were again haemolysed. Seventy-three patients not on SPS had unlysed repeat potassium, out of which 97.2% (71/73) had potassium ≤ 5.5 mmol/L. This indicates that haemolysis is a definite contributor to false hyperkalaemia. [Figure 1](#) shows that among all the non-haemolysed specimens, 40.3% (1216 cases) did not repeat serum potassium within 8 days. Of those who repeated and were not prescribed SPS, 86.4% (1362/1575) had false hyperkalaemia. Only 0.02% of patients had more than one repeat potassium within 8 days of index case.

In total, 1575 cases of repeat non-haemolysed potassium were done in the space of 2 years, and they were not prescribed SPS. All these cases were analysed in [tables 1 and 2](#) for factors associated with true- and false-hyperkalaemia. [Figure 1](#) shows the flow chart of cases included in this study.

Patients with unlysed repeat potassium within 8 days who were not prescribed SPS were univariately analysed for factors that is associated with true hyperkalaemia. As shown in [table 1](#), there were a total of 1575 patients, consisting of slightly more females than males, with a median age of 67 years and a median BMI of 24.5 kg/m².

Table 1 Factors associated with true hyperkalaemia*

	Total	True hyperkalaemia (K>5.5)	Normal (K≤5.5)	P-value
Total	1575 (100.0)	213 (13.5)	1362 (86.5)	
Gender				0.536
Female	837 (53.1)	109 (13)	728 (87)	
Male	738 (46.9)	104 (14.1)	634 (85.9)	
Age (year), median (IQR)	67 (60–75)	70 (63–77.5)	67 (59–75)	<0.001
BMI (kg/m ²), median (IQR)	24.5 (22–27.5)	24.1 (22–27.7)	24.5 (22–27.4)	0.682
eGFR (ml/min/m ²), median (IQR)	73.3 (48.7–92.5)	54.4 (35–82.1)	75.9 (51.4–94)	<0.001
Level of eGFR				<0.001
<30	147 (9.3)	38 (25.9)	109 (74.1)	
30–59	448 (28.4)	90 (20.1)	358 (79.9)	
60–89	530 (33.7)	51 (9.6)	479 (90.4)	
≥90	450 (28.6)	34 (7.6)	416 (92.4)	
On ARB				0.069
Yes	436 (27.7)	70 (16.1)	366 (83.9)	
No	1139 (72.3)	143 (12.6)	996 (87.4)	
On ACE-i				0.001
Yes	366 (23.2)	68 (18.6)	298 (81.4)	
No	1209 (76.8)	145 (12)	1064 (88)	
On spironolactone				0.668
Yes	31 (2)	5 (16.1)	26 (83.9)	
No	1544 (98)	208 (13.5)	1336 (86.5)	
On potassium chloride				>0.999
Yes	22 (1.4)	3 (13.6)	19 (86.4)	
No	1553 (98.6)	210 (13.5)	1343 (86.5)	
On potassium citrate				>0.999
Yes	1 (0.1)	0 (0)	1 (100)	
No	1574 (99.9)	213 (13.5)	1361 (86.5)	
On NSAIDs				0.311
Yes	19 (1.2)	4 (21.1)	15 (78.9)	
No	1556 (98.8)	209 (13.4)	1347 (86.6)	
On ACE-i and NSAIDs				0.517
Yes	5 (0.3)	1 (20)	4 (80)	
No	1570 (99.7)	212 (13.5)	1358 (86.5)	
On ARB and NSAIDs				0.421
Yes	14 (0.9)	3 (21.4)	11 (78.6)	
No	1561 (99.1)	210 (13.5)	1351 (86.5)	

Significant P values of <0.05 are bolded

*True hyperkalaemia refers to all repeat non-haemolysed potassium of >5.5, who are not on SPS.

ACE-i, Angiotensin-Converting Enzyme-inhibitors; ARB, Angiotensin receptor blockers; BMI, body mass index; eGFR, estimated Glomerular Filtration Rate; NSAIDs, non-steroidal anti-inflammatory drugs; SPS, sodium polystyrene sulfonate.

Patients with older age, lower eGFR or those taking ACE-i were significantly correlated with higher percentage of true hyperkalaemia. 7.6% of patients with either no kidney disease or stage 1 kidney disease (eGFR ≥90 mL/min/1.73 m²) had true hyperkalaemia, in contrast to

25.9% of patients with stage 4 kidney disease or worse (eGFR <30 mL/min/1.73 m²). There was only one patient on potassium citrate.

A multivariate logistic regression analysis of factors associated with false hyperkalaemia as per [table 2](#), shows

Table 2 Factors associated with false-hyperkalaemia (normal potassium)

	OR (95% CI)	P value
Age (year), median (IQR)	0.99 (0.98 to 1.01)	0.476
Level of eGFR (mL/min/1.73 m ²)		
<30	1	–
30–59	1.44 (0.93 to 2.23)	0.106
60–89	3.07 (1.90 to 4.97)	<0.001
≥90	3.60 (2.03 to 6.39)	<0.001
On ACE-i		
Yes	0.76 (0.53 to 1.09)	0.141
No	1	–

Significant P values of <0.05 are bolded
ACE-i, Angiotensin-Converting Enzyme-inhibitors; eGFR, estimated glomerular filtration rate.

that the main factor associated with false-hyperkalaemia was an eGFR >60 mL/min/1.73 m² (eGFR 60–89 mL/min/1.73 m² OR 3.07, 95% CI 1.90 to 4.97, p≤0.001, eGFR >90 mL/min/1.73 m² OR 3.60, 95% CI 2.03 to 6.39, p≤0.001). Age, and being prescribed ACE-i, were not significantly associated with false hyperkalaemia.

All potassium samples processed by the central laboratory from August 2015 to August 2017 were analysed individually to assess the impact of lag-time in processing of specimen, to the resultant potassium value. This was done regardless of patients' prescribed medications. Based on [table 3](#), those with higher potassium (K≥6.0 mmol/L) are significantly more likely to have longer waiting time between sample collection to processing time, with a mean of 276 min or 4 hours 36 min, compared with those with lower potassium (K≤5.0 mmol/L) with a mean of 226 min or 3 hours 46 min.

The effect of thrombocytosis and leucocytosis on hyperkalaemia was analysed. Out of all the FBC's done within 6 months of before and after index case, there were only 10 patients who had white cell count (WCC)>20×10⁹ cells/L or platelet counts >500×10⁹ cells/L. Haemoglobin was in the mild anaemia to mild polycythaemia range, with haemoglobin ranging between 7.9×10⁹cells/L and 15.8×10⁹ cells/L. All these patients had non-haemolysed potassium ranging between 5.1 and 5.9 mmol/L. The degree of hyperkalaemia did not correlate with the severity of thrombocytosis or leucocytosis. None of the non-haemolysed index potassium exceeded 6.0 mmol/L, even when the platelet was 1159×10⁹ cells/L or when the WCC was 170×10⁹ cells/L. These were the highest value of WCC and platelet among these 10 patients.

The analytical imprecision in the laboratory where potassium samples are processed, stand in the range of up to 5%. This means for a potassium of ≥6.0mmol/L, analytical imprecision would be up to ±0.3mmol/L. Only 2.8% of individual potassium specimens collected over duration of the study had a value of ≥6.0mmol/L. For

Table 3 Factors associated with hyperkalaemia for individual potassium samples

	Potassium level				Linear regression		
	Total	<5.1	5.1–5.4	5.5–5.9	≥6.0	Beta coefficient	P value
Total (%)	26 674 (100)	2747 (10.3)	18 598 (69.7)	4584 (17.2)	745 (2.8)		
Blood sample haemolysis							<0.001
No	26 005 (97.5)	2682 (10.3)	18 243 (70.2)	4428 (17)	652 (2.5)		
Yes	669 (2.5)	65 (9.7)	355 (53.1)	156 (23.3)	93 (13.9)	0.195	<0.001
Lag time from sample collection to processing (minutes), mean (SD)	255 (211.4–304.8)	226.1 (185.8–265.4)	257.2 (212.9–305.2)	263.9 (219.2–314.4)	276 (228.3–328.4)	0.001	<0.001

Significant P values of <0.05 are bolded

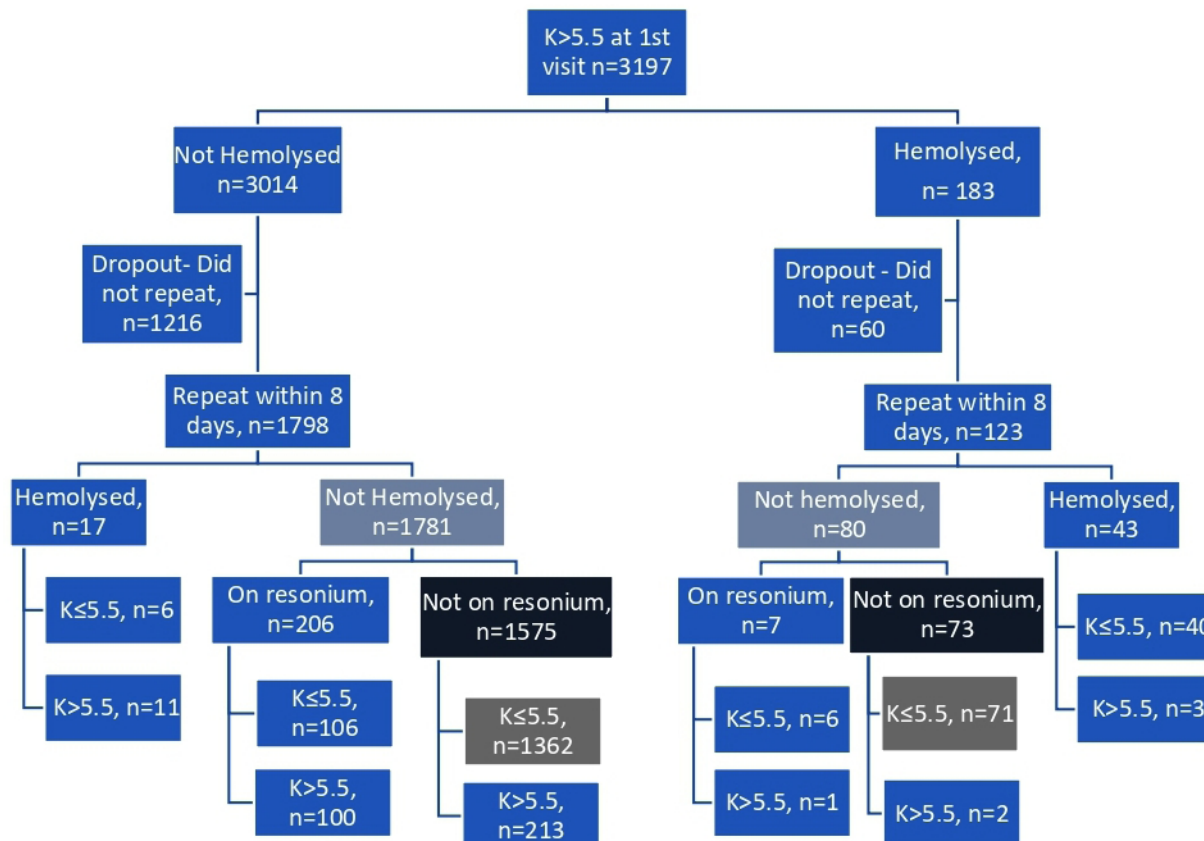


Figure 1 Flow chart of cases included in the study.

completeness of analysis, there were a total of 62 cases where the repeat potassium showed a difference of ± 0.1 mmol/L from the first potassium reading, and 118 cases for a difference of up to ± 0.2 mmol/L. Less than half of these contribute to incidences of false hyperkalaemia by this paper's definition (41.5% for ± 0.2 mmol/L, and 27.4% for ± 0.1 mmol/L). The distribution of difference between first and second potassium readings are as

shown in [figure 2](#), with the majority of repeat potassium exceeding the range of ± 0.2 mmol/L.

DISCUSSION

The prevalence of false hyperkalaemia in ambulatory clinics in Singapore is high at 86.4%. Only 13.6% of these patients have a warranted recall to repeat potassium.

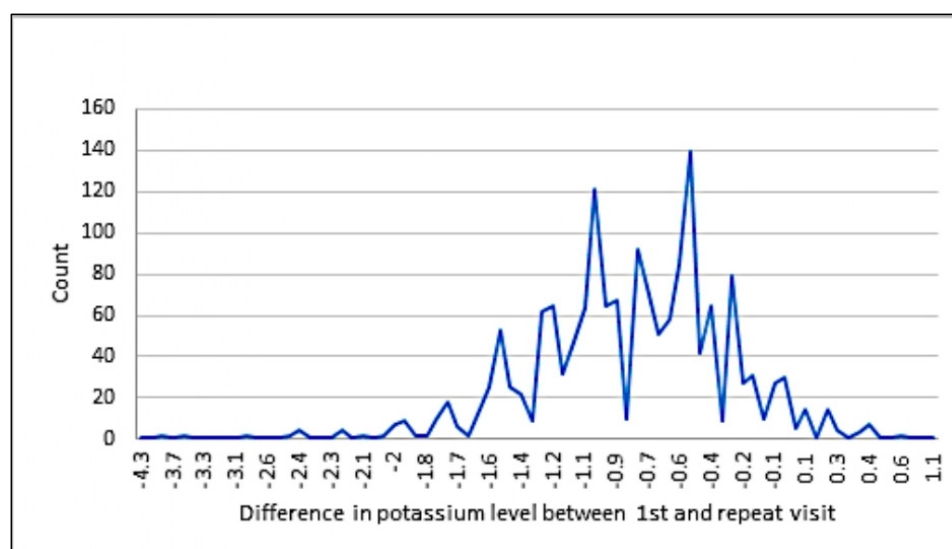


Figure 2 Distribution of difference in potassium level in mmol/L, between first and repeat visit, where $n = 1575$.

Although ACE-i, ARB, potassium-sparing diuretics and potassium replacements are known to cause hyperkalaemia, they were not a statistically significant factor for causing false or true hyperkalaemia. This could be possibly due to the time-lag to specimen processing being a more significant factor than medication ingestion. Another reason could be that prescribed dates, but not duration of treatment, were extracted during data mining. It is, therefore, difficult to determine with absolute certainty that patients were still taking the medications associated with hyperkalaemia when blood was drawn. It is also difficult to determine if these medications were stopped or reduced on patient receiving news of his or her hyperkalaemia, hence affecting repeat potassium levels. It is also possible that patients on ACE-i, ARB and potassium-sparing diuretics may have been counselled by healthcare providers to reduce the intake of high-potassium foods, especially if they have chronic kidney disease or have had previous episodes of hyperkalaemia. For patients on oral potassium chloride, patients are usually given potassium replacements because of preceding hypokalaemia. Hence, if these patients were adequately treated, they would not have overtreatment leading to hyperkalaemia. Additionally, centrifugation of serum potassium is done only for repeat standalone potassium samples. Centrifugation is not routinely done for the initial potassium samples that were collected as part of a hypertension, diabetes or renal panel.

A prospective study in an emergency department in New York showed that in the setting of haemolysis, eGFR >60 mL/min/ 1.73 m² in conjunction with a normal ECG is a reliable predictor of false hyperkalaemia, and may eliminate the need for repeat testing.¹⁶ Based on the results of this study, these factors hold true, and can be brought a step further. As $>90\%$ of patients with eGFR >60 mL/min/ 1.73 m² and 97.2% of patients with haemolysed potassium have false hyperkalaemia, in the presence of both haemolysis and CKD stage 2 or better, patients may omit repeat testing as long as they are asymptomatic.

An unpublished local institutional guide to managing hyperkalaemia is such that if patients have $K \geq 6.5$ mmol/L, regardless of sample haemolysis, they are called to present to the emergency department nearest to their home immediately for repeat testing. However, with this study results, the management guideline for hyperkalaemia can be improved. Whenever a patient with eGFR >60 mL/min/ 1.73 m² is reported to have unlysed potassium >5.5 mmol/L, the doctors can safely inform asymptomatic patients to repeat their potassium in the primary care setting within 1 week. Patients with CKD stage 3A or worse, however, should still have their repeat potassium done more urgently, be it in the emergency department if symptomatic, or within 1–2 days in the primary care setting if asymptomatic, as their chance of having true hyperkalaemia is increased.

Increased time-lag between specimen collection and processing is significantly associated with higher potassium levels. A delay of only 50 min seem to swing a patient

from a normal potassium value, to an emergency potassium value necessitating an emergency department attendance, thus increasing cost to the system. This finding is similar to a prospective trial done in a public tertiary care hospital in India, where mean potassium samples processed immediately at draw was 0.2 mmol/L lower than the very same potassium sample processed 3 hours after draw.⁸ That study suggested that potassium specimens should be centrifuged and processed in analyser within 1 hour. However, the electrolyte analyser and method used in that study differed from the analyser used in the polyclinic's central lab. The temperature in which the potassium specimens were kept also differed from the local setting. In order to mitigate the time-lag factor, more frequent courier services between polyclinics and central lab could be implemented, such that time-lag is kept to less than 3 hours. It is difficult to determine the optimal time lag between specimen collection to processing before the chance of false hyperkalaemia greatly increases in the local setting, as current specimens all have a processing time above 3 hours.

BMI does not correlate with false or true hyperkalaemia, which is in contrast to a retrospective case–control Japanese study which concluded that patients on ACE-i or ARB with a lower BMI are more prone to hyperkalaemia with $K > 5.5$ mmol/L.¹⁰ Patients on ACE-i are more likely to have true hyperkalaemia compared with those on ARB. Patients on neither ACE-i or ARB are more likely to have false hyperkalaemia.

Although spironolactone is a potassium-sparing diuretic, it is not significantly associated with true hyperkalaemia, in contrast to a study in Stockholm which showed that 18.5% of patients initiated on spironolactone developed an episode of $K > 5.0$ mmol/L within 3 months of initiation.¹⁷ This could be because locally, patients on spironolactone may have been educated for low potassium diet, as it is usually given as a fifth line antihypertensive, after ACE-i or ARB has been prescribed. The absolute number of patients on spironolactone in this study is also small.

Impact of false hyperkalaemia

The majority of polyclinic attendees are Singapore Citizens or Permanent Residents and enjoy government subsidies in their care. However, these subsidies do not occur in the emergency department setting unless patients were admitted inpatient thereafter. A typical polyclinic consult will cost a patient SGD 13.50, whereas a visit to any emergency department will cost the patient upwards of SGD 115. There are hidden costs incurred by concerned family members taking urgent leave to accompany patients to repeat potassium, and additional transport costs as well for the less mobile. An example of projected costs to a patient recalled for hyperkalaemia is appended in online supplementary annex A. Intangible costs to institution include time spent by nurses and doctors in recalling patients, who sometimes do not pick up their phone, necessitating repeat calls. Less educated and elderly patients may not understand instructions over



the phone. Short messaging service (SMS) and recall slips are sent to non-contactable patients with hyperkalaemia, increasing costs. Patients often worry and are anxious about their results.

Limitations of the study

Since this was a retrospective study, there were no data on food or supplements ingested by patients during the episodes of hyperkalaemia. Case notes were not reviewed for dietary assessment. Information on preanalytical variables, such as fist clenching, hyperventilation, EDTA contamination and postsplenectomy status, all of which increases the chance of false hyperkalaemia independent of time,⁴ was not available. It is also not known if patients consulted physicians or nurses for low potassium diet counselling, prior to repeating their serum potassium.

Some polyclinic patients were recalled to attend the nearest emergency departments, where immediate potassium results are available. However, potassium tests done in these emergency departments were unable to be captured in this study. The drop-out rate of 40.3% and 32.7% among the non-haemolysed and haemolysed arms, respectively, may have revealed other significant factors associated with true- and false-hyperkalaemia.

There is no international consensus as to what constitutes false hyperkalaemia.¹⁸ The definition of true hyperkalaemia as initial serum potassium of >5.5 mmol/L and a repeat potassium within 8 days of >5.5 mmol/L was used to aid clinical interpretation and relevant actions in managing these patients according to their risk profile. While there is a certain degree of measurement uncertainty to each serum potassium processed, this error will be present in all samples, and clinicians will still need to trust each potassium result published as-is, and manage patients based on guidelines.

CONCLUSIONS

In summary, the prevalence of unlysed false hyperkalaemia was 86.4% among ambulatory primary care patients in multiethnic Singapore. The main modifiable variable was a processing time delay of more than 50 min. The availability of in-house potassium analysers will reduce lag time and reduce the prevalence of false hyperkalaemia. The alternative of more frequent courier service such that all specimens can be processed within 3 hours of collection, should be considered. The results of this study can be generalised to most primary care practitioners in the private and public sectors all over the world, where the access to in-house potassium analysers are mostly limited, and potassium specimens mostly sit in the clinic for a few hours before they are despatched to a processing laboratory for analysis.

An eGFR 60 mL/min/ 1.73 m² significantly reduces the probability of true hyperkalaemia by more than three times that of a patient with eGFR <30 mL/min/ 1.73 m². This is similar to a Japanese study that showed that CKD stage 3A and worse is correlated with higher chances of

hyperkalaemia.¹⁹ Almost all patients with haemolysed potassium would have normal potassium. Only 2.8% of cases with haemolysed potassium has true hyperkalaemia. This should guide recall workflows such that patients with CKD stages 1 and 2 and patients with haemolysed potassium repeat potassium tests in the polyclinic rather than in the emergency department for cost-effectiveness. It is also warranted to repeat potassium test within 1–2 days if patient had a baseline of CKD stage 3A or worse, or if the creatinine rose concurrently with the rise in potassium.²⁰ In addition, risk calculators can be developed, to help clinicians decide on the need and urgency with which to repeat potassium. These can be further validated with future studies. Symptomatic patients regardless of severity of hyperkalaemia should still be advised to go to the emergency departments, for safety reasons. SPS should be given judiciously, and held back especially if the patient has a normal paired creatinine and FBC, and is not taking either ACE-i or ARB. It is important to screen the FBC for patients who have persistent hyperkalaemia despite normal creatinine, to exclude haematological malignancy.⁸

Areas for future research

A follow-up prospective case–control study can be done, with patients being their own control, where simultaneous serum potassium drawn is sent to both an in-house laboratory and an outhouse laboratory for processing. This way, the preanalytical factors for false hyperkalaemia can be balanced between both arms. Having a direct means of comparing the potassium values between an in-house laboratory and an outhouse laboratory will help determine the potential cost savings of having an in-house laboratory versus increasing the frequency of courier services to a central laboratory. An interinstitutional collaboration is needed to determine the true socioeconomic burden of false hyperkalaemia. As Singapore is building a few new polyclinics over the next few years, and with an ageing population where consumption and usage of laboratory services will increase, if the in-house lab is found to reduce the rate of false-hyperkalaemia, then all polyclinics should be planned with the intent and space for housing an in-house potassium analyser.

Twitter Alicia Ying Ying Boo @alicia_boomy@yahoo.com

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ORCID iDs

Alicia Ying Ying Boo <http://orcid.org/0000-0001-6099-3452>

Ngjap Chuan Tan <http://orcid.org/0000-0002-5946-1149>

REFERENCES

- Dans A, Ng N, Varghese C, *et al*. The rise of chronic non-communicable diseases in Southeast Asia: time for action. *Lancet* 2011;377:680–9.
- Couser WG, Remuzzi G, Mendis S, *et al*. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int* 2011;80:1258–70.
- Levis JT. Ecg diagnosis: hyperkalemia. *Perm J* 2013;17:69.
- Kroll MH, Elin RJ. Interference with clinical laboratory analyses. *Clin Chem* 1994;40:1996–2005.
- Turner HE, Peake RWA, Allison JJ. The impact of centrifugation in primary care on pseudohyperkalemia: a retrospective evaluation. *Ann Clin Biochem* 2013;50:371–3.
- Zaki KS, Majid U, Islam N. Spurious hyperkalaemia: an insight. *J Pak Med Assoc* 2011;61:297–9.
- Davis KR, Crook MA. Seasonal factitious increase in serum potassium: still a problem and should be recognised. *Clin Biochem* 2014;47:283–6.
- Baruah A, Goyal P, Sinha S, *et al*. Delay in specimen processing—major source of preanalytical variation in serum electrolytes. *J Clin Diagn Res* 2014;8:CC01–3.
- Sadjadi SA, McMillan JI, Jaipaul N, *et al*. A comparative study of the prevalence of hyperkalemia with the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. *Ther Clin Risk Manag* 2009;5:547–52.
- Hirai T, Yamaga R, Fujita A, *et al*. Low body mass index is a risk factor for hyperkalaemia associated with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers treatments. *J Clin Pharm Ther* 2018;43:829–35.
- Kardalas E, Paschou SA, Anagnostis P, *et al*. Hypokalemia: a clinical update. *Endocr Connect*
- Government of Singapore. Singapore Ministry of Health Primary Care Survey, 2014. Available: <https://www.moh.gov.sg/resources-statistics/reports/primary-care-survey-2014-report>
- Lepage L, Dufour A-C, Doiron J, *et al*. Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clin J Am Soc Nephrol* 2015;10:2136–42.
- Tran HA. Extreme hyperkalemia. *South Med J* 2005;98:729–32.
- Moore CR, Lin JJ, O'Connor N, *et al*. Follow-Up of markedly elevated serum potassium results in the ambulatory setting: implications for patient safety. *Am J Med Qual* 2006;21:115–24.
- Khodorkovsky B, Cambria B, Lesser M, *et al*. Do hemolyzed potassium specimens need to be repeated? *J Emerg Med* 2014;47:313–7.
- Trevisan M, de Deco P, Xu H, *et al*. Incidence, predictors and clinical management of hyperkalaemia in new users of mineralocorticoid receptor antagonists. *Eur J Heart Fail* 2018;20:1217–26.
- Palaka E, Grandy S, Darlington O, *et al*. Associations between serum potassium and adverse clinical outcomes: a systematic literature review. *Int J Clin Pract* 2020;74:e13421.
- Saito Y, Yamamoto H, Nakajima H, *et al*. Incidence of and risk factors for newly diagnosed hyperkalemia after hospital discharge in non-dialysis-dependent CKD patients treated with Ras inhibitors. *PLoS One* 2017;12:e0184402.
- Palevsky PM. Acute kidney injury: complications associated with acute kidney injury. nephrology hypertension, 2017. Available: <https://www.renalandurologynews.com/home/decision-support-in-medicine/nephrology-hypertension/acute-kidney-injury-complications-associated-with-acute-kidney-injury/>