

Appendix

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Electronic Supplementary Material

Intensity of Early Correction of Hyperglycemia and Outcome of Critically Ill Patients with Diabetic Ketoacidosis

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Methods

Calculations

We used the highest and lowest glucose (in mmol/L), sodium, and potassium levels as well as the highest urea level during the first 24 hours of ICU admission to calculate the highest and lowest plasma osmolarity:

Plasma osmolarity = 2(plasma sodium + plasma potassium) + Blood glucose +
Plasma urea

Additionally, we used the pH and PaCO₂ components of the Acute Physiology and Chronic Health Evaluation (APACHE) III score to calculate standard base excess (SBE) using the following formula:

$$\text{SBE} = 0.0279 \times \text{PaCO}_2 \times 10^{(\text{pH}-6.1)} + 13.8012 \times \text{pH} - 124.82088$$

Propensity Score Development

We determined each patient's probability of having a BGL >180 mg/dL using multivariable logistic regression modelling considering all pre-ICU variables. The propensity model was developed using stepwise selection and validated through backwards elimination procedures before undergoing a final assessment for clinical and biological plausibility (Table 1).

Diabetic Ketoacidosis Nested Cohort Analyses

From the source ANZICS APD cohort, we aimed to identify the 30 most recent DKA patients admitted from the ED to the ICU at the eight contributing hospitals. These hospitals were chosen as representing a mix of teaching and regional hospitals in at least three different states in Australia. In these patients we recorded all blood glucose levels, electrolyte levels and acid-base variables obtained from ED admission until ICU admission. In addition, we recorded insulin infusion rates, number and doses of insulin boluses, intravenous glucose administration and fluid administration. Finally, we compared blood glucose levels on ICU admission with highest blood glucose levels during the first 24 ICU hours.

Data were summarized as medians (interquartile ranges [IQR]) or as numbers (percentages). We used the sign-test of matched pairs to assess the difference between biochemical variables obtained on ED admission and ICU admission.

Diabetic Ketoacidosis Nested Cohort Results

We retrospectively screened 240 patients admitted to ICU with DKA at 8 hospitals. We excluded 21 patients who were admitted directly to ICU, in whom blood glucose levels in the ED were unrecordable, who were younger than 16 years of age, who had non-diabetic ketoacidosis, or in whom data from the ED admission were missing (Figure 3). Therefore, we studied 219 nested cohort patients of whom 87.7% had pre-admission insulin-requiring diabetes (Table 3). They were treated for a median of 4.6 (IQR, 3.2 to 6.6) hours in ED before ICU admission. Aspects of DKA treatment delivered in the ED were available in 197 (90.0%) patients and are presented in Table 4. The maximum intravenous insulin infusion rate was 5 (IQR, 5 to 7) units per hour corresponding to a weight-adjusted rate of 0.09 (IQR, 0.06 to 0.10) units per kg

per hour (in 125 patients with recorded body weight). Approximately one-third received one or more insulin boluses in ED. A total of 3000 (IQR, 2000 to 4000) ml of intravenous fluid were administered in ED at a median rate of 620 (IQR, 441 to 882) ml per hour with the majority receiving 0.9% Saline.

Such therapy decreased BGLs by 59 (IQR, 29 to 90) mg/dL per hour, increased plasma sodium by 0.9 (IQR, 0.2 to 1.8) mmol/L per hour and decreased plasma potassium by 0.2 (IQR, 0.1 to 0.3) mmol/L per hour. Consequently, plasma osmolarity decreased at a rate of 1.9 (IQR, 0.7 to 3.3) mmol/L per hour with a corresponding decrease in plasma tonicity of 1.6 (IQR, 0.6 to 2.8) mmol/L per hour. Metabolic acidosis and lactatemia significantly improved during ED admission (Table 5). The highest blood glucose level in ICU was obtained from the first blood sample in 152 (69.4%) patients. The mean difference between the first and highest blood glucose level in ICU was 30 (95% CI, 21 to 37) mg/dL. Outcomes of the nested cohort patients are presented in Table 6.

Tables

Table 1. Propensity Score Model

Variable	Highest Blood Glucose Level in the First 24 Hours		P Value*	Odds Ratio (95% CI)
	≤180 mg/dL No. (%)	>180 mg/dL No. (%)		
Age group			<0.001	
≤44 years	436 (72.1%)	5087 (64.0%)		0.87 (0.45 - 1.68)
45 to 64 years	101 (16.7%)	1918 (24.1%)		1.47 (0.74 - 2.90)
65 to 84 years	58 (9.6%)	821 (10.3%)		1.10 (0.55 - 2.22)
>84 years	10 (1.7%)	122 (1.5%)		1.00
Hospital			<0.001	
Metropolitan	267 (44.1%)	3092 (38.9%)		0.71 (0.57-0.89)
Private	27 (4.5%)	385 (4.8%)		0.82 (0.53-1.28)
Rural	134 (22.1%)	2362 (29.7%)		1.00
Tertiary	177 (29.3%)	2109 (26.5%)		0.69 (0.54-0.88)
State			<0.001	
Australian Capital Territory	24 (4.0%)	207 (2.6%)		0.47 (0.29-0.77)
New South Wales	254 (42.0%)	2955 (37.2%)		0.64 (0.49-0.83)
Northern Territory	8 (1.3%)	224 (2.8%)		1.46 (0.70-3.08)
New Zealand	18 (3.0%)	457 (5.7%)		1.17 (0.69-1.98)
Queensland	157 (26.0%)	1519 (19.1%)		0.47 (0.36-0.62)
South Australia	34 (5.6%)	544 (6.8%)		0.80 (0.52-1.22)
Tasmania	6 (1.0%)	157 (2.0%)		1.40 (0.60-3.28)
Victoria	87 (14.4%)	1680 (21.1%)		1.00
Western Australia	17 (2.8%)	205 (2.6%)		0.63 (0.36-1.10)
Time in hospital prior to ICU admission			<0.001	
<2.00 hours	159 (26.3%)	2099 (26.4%)		1.52 (1.18-1.95)
2.00 to 3.99 hours	106 (17.5%)	1884 (23.7%)		1.92 (1.47-2.52)
4.00 to 5.99 hours	129 (21.3%)	1685 (21.2%)		1.39 (1.07-1.79)
6.00 to 7.99 hours	76 (12.6%)	942 (11.9%)		1.30 (0.97-1.75)
≥8.00 hours	135 (22.3%)	1338 (16.8%)		1.00
*Chi-square test				
SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.				

Table 2. Sensitivity Analysis I

Table 2. Adjusted Odds Ratios for Hypoglycemia, Hypokalemia, Hypoosmolarity and Hospital Mortality in the Full Diabetic Ketoacidosis Cohort.								
Variable	Hypoglycemia*		Hypokalemia†		Hypoosmolarity‡		Hospital Mortality	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Highest blood glucose level in the first 24 ICU hours, mmol/l		<0.001		0.001		<0.001		0.12
≤10.0	2.12 (1.67-2.69)		0.78 (0.61-0.99)		1.24 (1.01-1.53)		2.35 (1.11-5.01)	
10.1 to 20.0	1.00		1.00		1.00		1.00	
20.1 to 30.0	0.67 (0.55-0.81)		0.80 (0.69-0.93)		0.85 (0.74-0.98)		0.96 (0.52-1.75)	
30.1 to 40.0	0.48 (0.35-0.67)		0.63 (0.49-0.81)		1.03 (0.83-1.27)		1.39 (0.72-2.69)	
>40.0	0.37 (0.26-0.54)		0.85 (0.67-1.10)		1.67 (1.33-2.09)		0.95 (0.49-1.83)	
ANZROD, per %	0.99 (0.97-1.02)	0.61	1.03 (1.01-1.04)	<0.001	0.99 (0.96-1.01)	0.22	1.11 (1.09-1.13)	<0.001
Admission year, per year	1.00 (0.97-1.03)	0.99	0.97 (0.95-0.99)	0.001	0.99 (0.97-1.01)	0.26	0.90 (0.85-0.96)	<0.001
Propensity for glucose >10 mmol/l, per %	1.00 (0.96-1.04)	0.99	0.95 (0.92-0.98)	<0.001	0.97 (0.94-0.99)	0.007	1.02 (0.94-1.11)	0.57
Urea, per mmol/l	1.00 (0.99-1.01)	0.92	0.96 (0.95-0.98)	<0.001	0.85 (0.84-0.87)	<0.001	1.03 (1.01-1.05)	0.006
Non insulin-dependent diabetes	1.00		1.00		1.00		1.00	
Insulin-dependent diabetes	1.33 (1.11-1.59)	0.002	0.62 (0.54-0.71)	<0.001	1.03 (0.91-1.17)	0.64	0.58 (0.38-0.88)	0.01
Plasma creatinine level, µmol/l		0.58		0.005		<0.001		0.001
<100	1.00		1.00		1.00		1.00	
100 to 129	0.87 (0.70-1.09)		0.75 (0.63-0.90)		0.86 (0.73-1.01)		1.13 (0.52-2.46)	
130 to 159	0.93 (0.69-1.25)		0.72 (0.56-0.92)		1.20 (0.95-1.50)		2.11 (0.99-4.51)	
160 to 219	0.90 (0.64-1.26)		0.77 (0.58-1.02)		1.27 (0.97-1.67)		3.80 (1.95-7.40)	
>219	1.11 (0.77-1.61)		1.01 (0.73-1.40)		3.04 (2.18-4.23)		3.37 (1.69-6.73)	
Missing Data	1.51 (0.62-3.72)		1.01 (0.32-3.14)		1.24 (0.42-3.64)		1.41 (0.26-7.77)	

ANZROD, Australian and New Zealand Risk of Death model with glucose components removed
 *Blood Glucose Level <4 mmol/l (<72 mg/dl) †Plasma Potassium Level <3.3 mmol/l ‡Plasma Osmolarity <285 mmol/l

Table 3. Sensitivity Analysis II

Table 3. Adjusted Odds Ratios for Hypoglycemia, Hypokalemia, Hypoosmolarity and Death in the Full Diabetic Ketoacidosis Cohort Patients With Highest Blood Glucose Level >180 mg/dL.								
	Hypoglycemia ^a		Hypokalemia ^b		Hypoosmolarity ^c		Hospital Mortality	
Variable	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Highest blood glucose level in the first 24 hours		<0.001		<0.001		<0.001		0.61
181 to 360 mg/dL	1.00		1.00		1.00		1.00	
361 to 540 mg/dL	0.67 (0.55-0.81)		0.79 (0.68-0.92)		0.85 (0.74-0.98)		0.96 (0.53-1.77)	
541 to 720 mg/dL	0.48 (0.35-0.66)		0.62 (0.48-0.80)		1.03 (0.84-1.28)		1.42 (0.74-2.74)	
>720 mg/dL	0.35 (0.24-0.51)		0.86 (0.67-1.11)		1.71 (1.36-2.16)		1.00 (0.52-1.92)	
ANZROD, %	0.99 (0.97-1.02)	0.58	1.03 (1.01-1.04)	<0.001	0.99 (0.97-1.01)	0.33	1.11 (1.09-1.13)	<0.001
Admission year, y	1.00 (0.98-1.03)	0.87	0.96 (0.94-0.98)	<0.001	0.98 (0.97-1.00)	0.08	0.91 (0.86-0.97)	0.004
Urea, mmol/L	1.00 (0.98-1.01)		0.96 (0.94-0.97)	<0.001	0.85 (0.83-0.86)	<0.001	1.03 (1.01-1.05)	0.007
Insulin-dependent diabetes	1.42 (1.17-1.73)		0.62 (0.54-0.72)	<0.001	1.03 (0.90-1.18)	0.67	0.55 (0.36-0.85)	
Plasma creatinine level		0.23		0.008		<0.001		0.005
<100 µmol/L	1.00		1.00		1.00		1.00	
100 to 129 µmol/L	0.86 (0.68-1.08)		0.75 (0.62-0.91)		0.84 (0.71-1.00)		1.35 (0.60-3.07)	
130 to 159 µmol/L	0.92 (0.67-1.26)		0.74 (0.58-0.96)		1.15 (0.91-1.45)		2.47 (1.11-5.50)	
160 to 219 µmol/L	0.95 (0.67-1.36)		0.74 (0.55-0.99)		1.29 (0.98-1.71)		3.84 (1.84-7.99)	
>219 µmol/L	1.35 (0.91-1.99)		1.00 (0.71-1.41)		2.73 (1.94-3.85)		3.59 (1.69-7.62)	
Missing Data	1.50 (0.58-3.88)		1.39 (0.44-4.39)		1.67 (0.52-5.32)		1.56 (0.30-8.11)	

Abbreviations: ANZROD, Australian and New Zealand Risk of Death model with glucose components removed
^aBlood glucose level <72 mg/dL
^bPlasma potassium level <3.3 mmol/L
^cPlasma osmolarity <285 mmol/L
SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.

Table 4. Characteristics of Nested Cohort Patients

Characteristic	Nested Cohort (N = 219)
Age – yr	38 (25-52)
Males – no. (%)	98 (44.8)
Weight – kg (n = 125)	69 (60-82)
Diabetes type – no. (%)	
Type 1	161 (73.5)
Type 2	34 (15.5)
Unknown	24 (11.0)
Insulin-dependent diabetes – no. (%)	192 (87.7)
Values are median (IQR) or n (%)	

Table 5. Treatment of Nested Cohort Patients in ED

Therapy	Nested Cohort (N = 197)
Insulin infusion	
Max rate – units/hour (N = 197)	5 (5-7)
Max rate – units/kg/hour (N = 125)	0.09 (0.06-0.10)
Insulin bolus – no. (%)	
0	132 (67.0)
1	60 (30.5)
2	4 (2.0)
3	1 (0.5)
Total bolus dose in treated – units (n = 65)	10 (6-10)
Fluid input	
Total fluid input – ml (n = 197)	3000 (2000-4000)
Rate of fluid administration – ml/hour (n = 197)	629 (441-882)
Fluid type – no. (%)	
0.9% Saline	174 (88.3)
Hartmann's Solution	42 (21.3)
Plasma-Lyte 148®	18 (9.1)
Colloid solution	2 (1.0)
Glucose infusion commenced in ED – no. (%)	34 (17.3)
Values are median (IQR) or n (%)	

Table 6. Biochemical Changes in Nested Cohort Patients

Table 5. Changes in biochemical variables between emergency department admission and intensive care unit admission in the nested cohort^a.

Variable	First value in Emergency Department Median (IQR)	First value in Intensive Care Unit Median (IQR)	Increase (+) or Decrease (-) Median (IQR)	P value ^b	Rate of Increase (+) or Decrease (-) Median (IQR) unit/hr
Blood Glucose Level – mg/dL	684 (486 to 882)	347 (232 to 576)	-268 (-432 to -146)	<0.001	-59 (-90 to -29)
Plasma Sodium – mmol/L	133 (128 to 137)	137 (134 to 140)	4 (1 to 8)	<0.001	0.9 (0.2 to 1.8)
Plasma Potassium – mmol/L	5.4 (4.7 to 6.2)	4.3 (3.9 to 4.8)	-1.0 (-1.7 to -0.4)	<0.001	-0.2 (-0.3 to -0.1)
Plasma Osmolarity – mmol/L ^c	325 (312 to 339)	315 (302 to 333)	-9.6 (-16 to -2.9)	<0.001	-1.9 (-3.3 to -0.7)
Plasma Tonicity – mmol/L ^d	313 (304 to 323)	303 (294 to 317)	-8.0 (-14 to -2.5)	<0.001	-1.6 (-2.8 to -0.6)
Plasma Chloride – mmol/L	99 (92 to 105)	112 (107 to 116)	12 (7 to 17)	<0.001	2.4 (1.4 to 3.7)
Plasma Bicarbonate – mmol/L	6 (5 to 10)	9 (6 to 14)	2 (0 to 5)	<0.001	0.4 (0 to 0.9)
Plasma Base Excess – mmol/L	-25 (-29 to -20)	-18 (-24 to -12)	4.8 (1.6 to 9.3)	<0.001	1.0 (0.4 to 1.8)
Lactate – mmol/L	3.1 (2.1 to 4.3)	1.5 (1.0 to 2.6)	-1.3 (-2.2 to -0.4)	<0.001	-0.2 (-0.5 to -0.1)
Arterial pCO ₂ – mmHg	22 (17 to 29)	23 (16 to 31)	-1 (-6 to 4)	0.31	-0.2 (-1.4 to 0.8)
pH	7.02 (6.91 to 7.12)	7.21 (7.10 to 7.29)	0.15 (0.08 to 0.24)	<0.001	0.03 (0.02 to 0.05)

^aMedian (IQR) time between emergency department admission and intensive care unit admission was 4.6 (3.2 to 6.6) hours

^bTwo-sided comparison between first value in emergency department and first value in intensive care unit using sign-test of matched pairs

^cCalculated as: 2(plasma sodium + plasma potassium) + Blood glucose + Plasma urea

^dCalculated as: 2(plasma sodium + plasma potassium) + Blood glucose

SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.

Table 7. Outcomes of Nested Cohort Patients

Outcome	Nested Cohort (N = 219)
Hypoglycemia – no. (%) ^a	0
Hypokalemia – no. (%) ^b	20/210 (9.5)
Hypoosmolarity – no. (%) ^c	4/203 (2.0)
ICU length of stay – days	1.9 (1.0-2.4)
Hospital length of stay – days	4.0 (2.5-7.0)
ICU mortality – no. (%)	0
Hospital mortality – no. (%)	2 (0.9)
Values are median (IQR) or n (%)	
^a Blood glucose level <72 mg/dl	
^b Plasma potassium level <3.3 mmol/L	
^c Plasma osmolarity <285 mmol/L	
SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.	

Figures

Figure 1. Highest Glucose ≤180 mg/dL by Year

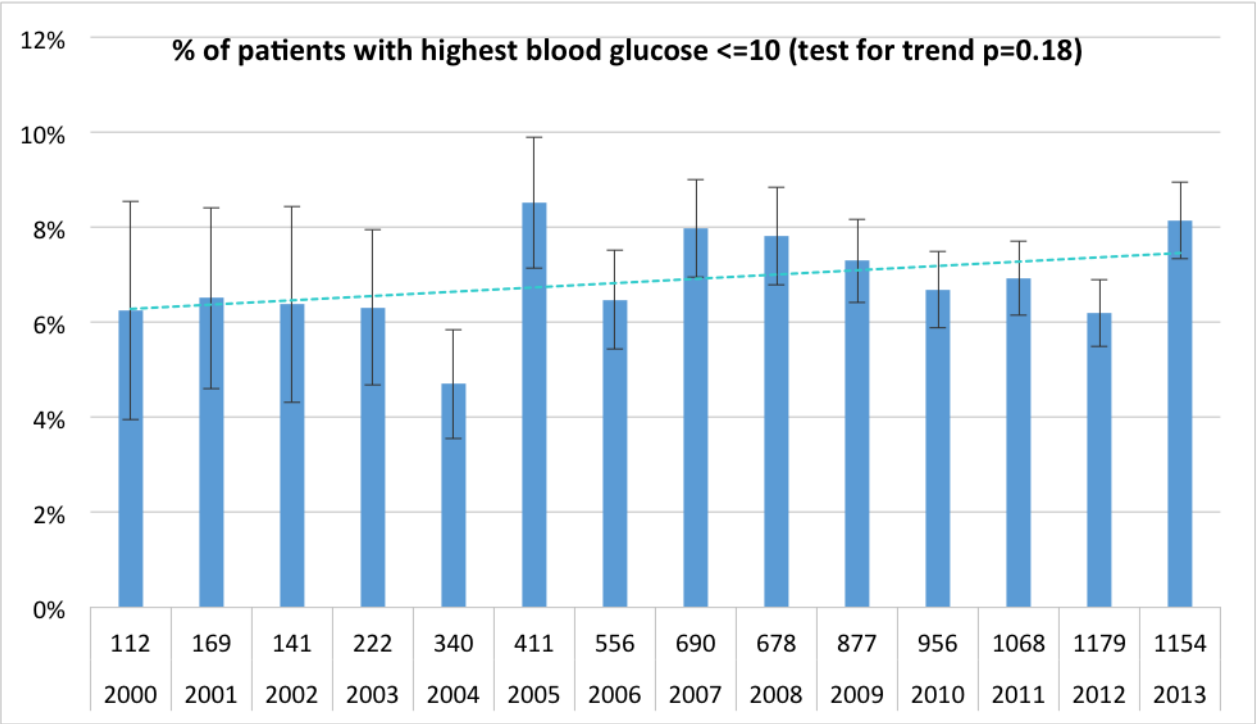
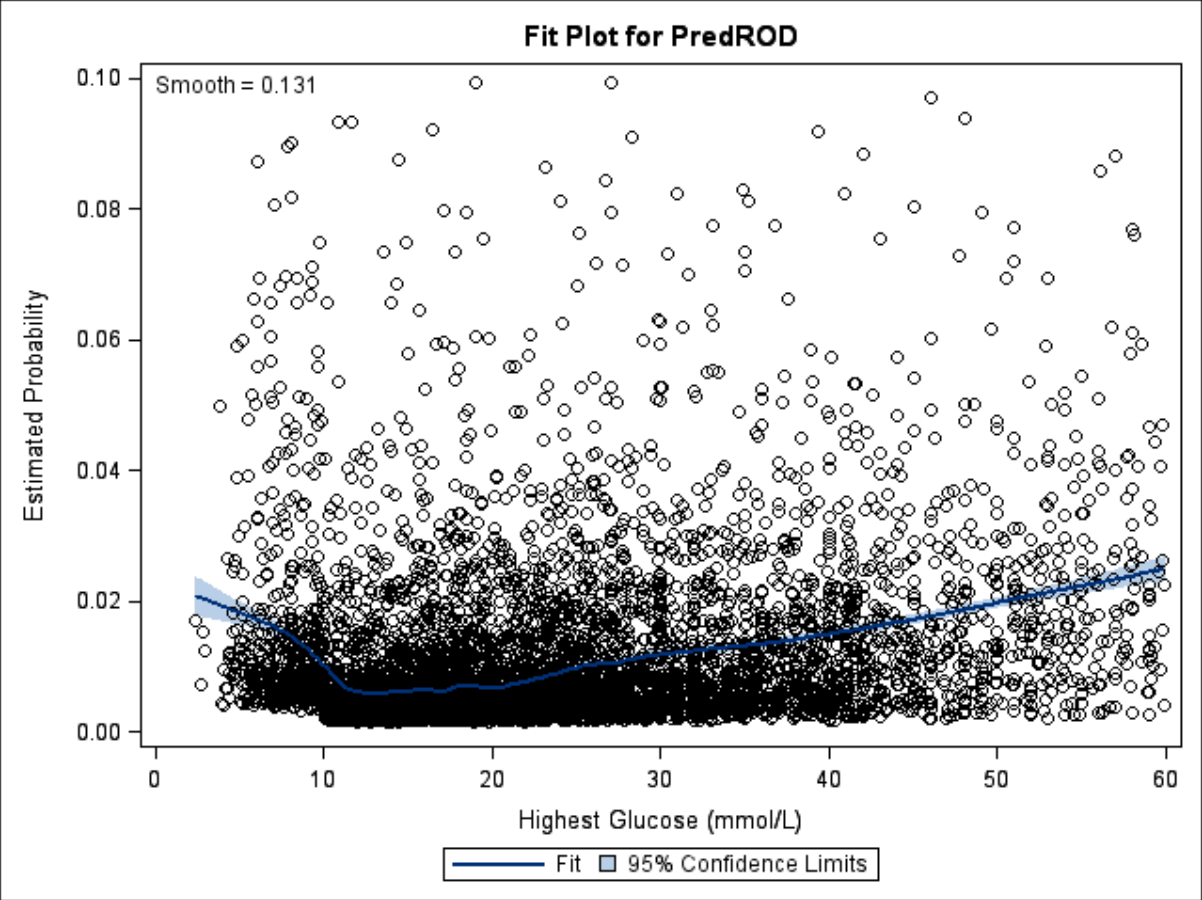


Figure 2. Highest Glucose vs. Predicted Risk of Death



SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.

Figure 3. Selection of Nested Cohort Patients

