Characterising frailty, metrics of continuous glucose monitoring, and mortality hazards in older adults with type 2 diabetes on insulin therapy (HARE): a prospective, observational cohort study

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Summary

Background To our knowledge, no previous study has examined the inter-relationship between frailty, dysglycaemia, and mortality in frail older adults with type 2 diabetes who are on insulin therapy. We used continuous glucose monitors (CGMs) to profile this patient population and determine the prognostic value of CGM metrics. We hypothesised that incremental frailty was associated with increased hypoglycaemia or time below range (TBR).

Methods HARE was a multicentre, prospective, observational cohort study with mortality hazard analysis carried out in four hospitals in Hong Kong. Eligible participants were community-living adults aged 70 years and older; had had type 2 diabetes for 5 years or more; were on insulin therapy; were frail; and were not hospitalised at the time of frailty assessment and CGM recording. Glucose control was characterised according to the Advanced Technologies and Treatments for Diabetes 2019 international consensus clinical targets. Frailty index was computed, and comprehensive frailty assessments and targeted serum metabolic profiling were performed. The Jonckheere-Terpstra test for trend was used to analyse frailty index tertiles and variables. Inter-relationships between CGM metrics and frailty, glycated haemoglobin A_{1c} (HbA_{1c}), and serum albumin were characterised using adjusted regression models. Survival analysis and Cox proportional hazard modelling were performed.

Findings Between July 25, 2018, and Sept 27, 2019, 225 participants were recruited, 222 of whom had CGMs fitted and 215 of whom had analysable CGM data (190 were frail, 25 were not frail). Incremental frailty was associated with older age, greater HbA_{1c}, worse renal function, and history of stroke. Eight of 11 CGM metrics were significantly associated with frailty. Decreased time in range (TIR; glucose concentration 3·9–10·0 mmol/L) and increased time above range (TAR) metrics were strongly correlated with increased frailty and hyperglycaemia, whereas TBR metrics were marginally or not different between frailty levels. Glucose-lowering agents did not significantly affect regression estimates. In patients with HbA_{1c} of 7·5% or more, reduced serum albumin was associated with level 2 TAR (glucose concentration >13·9 mmol/L) and dysglycaemia. During a median follow-up of 28·0 months (IQR 25·3–30·4), increased level 2 TAR was predictive of mortality explainable by frailty in the absence of detectable interaction. Each 1% increment of level 2 TAR was associated with 1·9% increase in mortality hazard.

Interpretation In older adults with type 2 diabetes who are on insulin therapy, incremental frailty was associated with increased dysglycaemia and hyperglycaemia rather than hypoglycaemia. Mortality hazard was increased with severe hyperglycaemia. Future clinical studies and trials targeting actionable CGM metrics highlighted in this study could translate into improved care and outcomes.

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Introduction

Projections from the 2017 Global Burden of Disease Study[1] and other estimates[2] suggest that the number of people with diabetes is between 500 and 600 million. The impact of diabetes on the older adult population is a global challenge to healthy ageing, and frailty is emerging as a recognised complication of diabetes.[3] Frailty might be present in 32–48% of older adults with diabetes,[4] and is associated with increased risks for disability, hospital admission, and death.[5] Frailty is an ageing-related clinical syndrome characterised by a reduction in systemic physiological reserve, multimorbidity, increased vulnerability to disease, and heightened risks for future hospital admission and death.[5,6] The adverse interaction between frailty and diabetes is compounded by disease complications,

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Research in context

Evidence before this study

The inter-relationship between frailty and dysglycaemia, or poor control of blood glucose (hypoglycaemia, hyperglycaemia, or both), in older adults with diabetes is poorly understood. Dysglycaemia can exacerbate frailty and is associated with medical complications. Towards individualised diabetes care and management, two studies in 2020 found benefits of continuous glucose monitors (CGMs) in the management of type 1 diabetes in older adults. A randomised clinical trial (NCT03240432) compared CGM versus standard capillary blood glucose monitoring and found improved glucose control in the CGM group, whereas an observational study (NCT03078491) identified specific standardised metrics of CGM that indicated increased risks of hypoglycaemia. However, in older adults with type 2 diabetes who are on insulin therapy, the role of CGMs and the impact of frailty on glucose concentrations is unclear.

Added value of this study

Our cohort study of predominantly frail older adults with type 2 diabetes who are on insulin therapy showed the inter-relationships between frailty and glucose control, particularly in a pattern of increased hyperglycaemia. One of the standardised metrics of CGM, level 2 time above range (TAR; defined by glucose concentration >13·9 mmol/L), was found to be a significant independent predictor of future mortality (1·9% increase in mortality hazard per 1% increase in level 2 TAR). Further analysis identified frailty as an explanatory factor for this mortality hazard.

Implications of all the available evidence

This study has linked frailty with hyperglycaemia and dysglycaemia to a greater extent than with hypoglycaemia, and identified a novel, prognostic CGM marker in frail older adults with type 2 diabetes who require insulin. Future clinical trials are needed to compare and identify therapeutic regimens and treatments for type 2 diabetes that are associated with reversal of frailty as a primary clinical endpoint while maintaining guideline-recommended CGM targets.

accumulation of disabilities, and potentiating effects of dysglycaemia and chronic hyperglycaemia that further promote frailty and adverse outcomes.[3–7]

Although the relationship between frailty and glucose control is unclear, accumulating evidence suggests that chronic hyperglycaemia might potentiate frailty.[7] Although the landmark findings from Action to Control Cardiovascular Risk in Diabetes (ACCORD)[8] and other studies have shifted the focus away from strict glucose control owing to increased mortality risks and harms observed, the strive towards euglycaemia to reduce long-term diabetic vascular complications as demonstrated in the UK Prospective Diabetes Study (UKPDS)[9] has been tempered. Moreover, the use of insulin in patients with diabetes has raised concerns due to potential harms and adverse outcomes from hypoglycaemia;[10–12] although it is possible that hypoglycaemia is both a contributor to adverse outcomes and a marker of susceptibility to such events.[13]

The management of older adults with diabetes requires individualised assessment as well as titration of care and medications that balances treatment efficacy, safety, secondary prevention of complications, quality of life, and goals of care.[3,14,15] The current level and strength of evidence for managing diabetes in older adults with frailty are limited. For example, although individualised upward adjustment of glycated haemoglobin A_{1c} (HbA_{1c}) targets in 0·5% increments (eg, 7·5%, 8·0%, 8·5%) is recommended for older adults with increased disease complexity and comorbidities,[15] the evidence base for such recommendations and the means by which the targets can be met are uncertain. Similarly, a proposed management framework has categorised older adults with frailty and diabetes as having poor health (group 3), necessitating shared decision making for glucose target ranges and therapeutic options among health professionals.[14] However, an instructive algorithm or pathway for individualised management was not detailed. The daunting task of managing older adults with diabetes has been highlighted previously.[3]

Continuous glucose monitors (CGMs) can provide more comprehensive glycaemic profiling that yields clinically actionable information for tailoring diabetes care and management and might provide a data-driven approach in glycaemic control. A randomised clinical trial by Pratley and colleagues[16] showed that CGMs improved glycaemic control and reduced hypoglycaemia in patients with type 1 diabetes. However, the use of CGMs in patients with type 2 diabetes is poorly defined despite evidence suggesting improvement in patients' treatment adherence and lifestyle.[17] In a study by Toschi and colleagues,[18] specific CGM metrics, including glucose variability and the glucose management indicator,[19] were found to be informative in identifying older adults with type 1 diabetes at high risk of hypoglycaemia.[20] Whether those indicators are useful and provide prognostic information on survival in patients with type 2 diabetes is unknown. Therefore, in this multicentre, observational study of older, community-based patients with type 2 diabetes and borderline frailty who were on insulin therapy, we aimed to use CGMs to (1) characterise the relationship between frailty and glycaemic control, (2) determine if future mortality can be predicted by CGM metrics, and (3) perform targeted metabolic profiling to identify non-glycaemic determinants of glucose control. We hypothesised that frailty was associated with increased

frequency of hypoglycaemia, and that specific CGM metrics (eg, time below range [TBR]) were predictive of mortality.

Methods

Study design and participants

HARE was a multicentre, prospective, observational cohort study done in outpatients from four hospitals (Prince of Wales Hospital, Shatin Hospital, Alice Ho Miu Ling Nethersole Hospital, and Tai Po Hospital) in Hong Kong. Eligible participants were community-living adults aged 70 years and older; attendees of general medical or diabetes clinics; had had type 2 diabetes for 5 years or longer; were on insulin therapy with no intention to stop within 1 year; were frail; and were not hospitalised at the time of frailty assessment and during CGM recording. Individuals with scores of 3–5 (out of 5 maximum) on the Fatigue, Resistance, Ambulation, Illness, and Loss of weight (FRAIL) scale[21] on telephone screening were considered to be frail and invited for interview in person. Exclusion criteria were active, untreated endocrinopathies; estimated glomerular filtration rate (eGFR by Chronic Kidney Disease Epidemiology Collaboration equation) of less than 15 mL/min per 1·73 m²; advanced dementia; Mobitz type II, high-grade second-degree or complete heart block; presence of a permanent pacemaker or implantable cardioverter defibrillator; anti-arrhythmic drug therapy; use of major tranquilisers; and terminal illness with expected survival of less than 1 year. All participants provided written informed consent. The study complied with the Declaration of Helsinki and was approved by the local institutional review board (CUHK-NTEC Clinical Research Ethics Committee, study number 2017.702).

Continuous interstitial glucose monitoring

The iPro2 Professional CGM (Medtronic, Minneapolis, MN, USA) was used according to manufacturer's instructions. All CGMs were fitted by the same professionally trained research nurse according to protocol. CGM readings were characterised according to the Advanced Technologies and Treatments for Diabetes (ATTD) 2019 international consensus document on clinical targets for CGM interpretation.[20] The 11 CGM metrics used in our study included mean glucose concentration, mean amplitude of glucose excursion, and nine others (coefficient of glycaemic variability, glucose management indicator, time above range [TAR], level 1 TAR, level 2 TAR, time in range [TIR], TBR, level 1 TBR, and level 2 TBR; these CGM metrics are further defined in appendix p 4).

Frailty assessments

We used the 40-item frailty index by Rockwood and Mitniski,[22] which is based on the cumulative deficit model that computed the ratio of the number of medical comorbidities or deficits to the total number of inventory items assessed. Patients' self-reported information was collected at interview in person, cross-checked, and combined with available relevant information in the electronic health record system. To classify frail and non-frail individuals, we used a cutpoint of 0·125 computed from integers (five of 40 deficits) that closely approximated that of Clegg and colleagues[23] (0·12; appendix p 5). Clegg and colleagues' cutpoint is based on validated analyses of more than 900 000 community-dwelling older adults (mean age 75·0 years [SD 7·2]) in whom the hazards for hospitalisation, mortality, and nursing home admission had been estimated.[23] To assess cognitive function, we used a validated Hong Kong Chinese version of the Montreal Cognitive Assessment (HK-MoCA) with unchanged contents, structure, and scoring system; in the HK-MoCA, mild cognitive impairment is indicated by a score of less than 22 out of 30, rather than less than 26 out of 30 as is used in the original MoCA.[24] Physical capacity and function were assessed using the Physical

See Online for appendix

	Total (n=215)	Tertiles of frailty index			p value*
		Lowest (n=73)	Middle (n=82)	Uppermost (n=60)	
Age, years	74 (71–78)	71 (69–76)	74 (71–77)	77 (73–82)	<0·0001
Sex					
Female	104 (48%)	31 (43%)	40 (49%)	33 (55%)	0·15
Male	111 (52%)	42 (57%)	42 (51%)	27 (45%)	..
Body-mass index, kg/m²	25·9 (23·2–28·9)	25·7 (22·8–27·9)	26·0 (23·6–29·0)	26·1 (24·0–28·6)	0·31
Weight, kg	65·4 (58·4–74·4)	64·2 (57·5–74·0)	67·1 (59·8–74·4)	62·8 (55·7–74·5)	0·67
Duration of diabetes, years	22·1 (8·6)	21·0 (9·3)	23·4 (7·7)	21·6 (9·0)	0·76
HbA_{1c}					
HbA_{1c}, %	8·2% (7·4–9·0)	7·8% (7·1–8·8)	8·3% (7·6–9·0)	8·2% (7·6–9·3)	0·042
HbA_{1c}, mmol/mol	66·1 (57·4–74·9)	61·7 (54·1–72·7)	67·2 (59·6–74·9)	66·1 (59·6–78·1)	..
eGFR, mL/min per 1·73 m²	46·3 (29·2–67·8)	55·2 (33·5–80·0)	47·1 (29·3–69·1)	34·5 (28·7–48·9)	0·0008
Smoking status					
Never	199 (93%)	71 (97%)	72 (88%)	56 (93%)	0·33
Former	15 (7%)	2 (3%)	9 (11%)	4 (7%)	0·32
Active	1 (<1%)	0	1 (1%)	0	0·94
Comorbidities					
Hypertension	190 (88%)	62 (85%)	74 (90%)	54 (90%)	0·34
Chronic kidney disease†	129 (60%)	38 (52%)	47 (57%)	44 (73%)	0·14
Stroke	60 (28%)	10 (14%)	22 (27%)	28 (47%)	<0·0001
Coronary artery disease	41 (19%)	13 (18%)	11 (13%)	17 (28%)	0·15
Cancer	35 (16%)	13 (18%)	15 (18%)	7 (12%)	0·36
Heart failure	27 (13%)	10 (14%)	5 (6%)	12 (20%)	0·34
Atrial fibrillation or atrial flutter	23 (11%)	7 (10%)	7 (9%)	9 (15%)	0·34

(Table 1 continues on next page)

	Total (n=215)	Tertiles of frailty index			p value*
		Lowest (n=73)	Middle (n=82)	Uppermost (n=60)	
(Continued from previous page)					
Global frailty assessments					
Frailty index	0·2 (0·2–0·3)	0·1 (0·1–0·2)	0·2 (0·2–0·2)	0·3 (0·3–0·4)	..
HK-MoCA‡	22 (18–25)	23 (20–26)	23 (19–26)	19 (14–23)	<0·0001
PASE	51 (11–62)	59 (34–82)	55 (30–59)	7 (2–31)	<0·0001
IADL	8 (5–8)	8 (6–8)	8 (7–8)	5 (3–7)	<0·0001
SF-12	0·2 (0·2–0·3)	0·1 (0·1–0·2)	0·2 (0·2–0·2)	0·3 (0·3–0·4)	0·0079
6MWD, m	281 (203–337)	342 (286–372)	277 (212–315)	190 (60–256)	<0·0001
Gait speed, m/s	0·74 (0·57–0·89)	0·86 (0·75–1·00)	0·73 (0·57–0·86)	0·56 (0·39–0·69)	<0·0001
Handgrip strength/ body-mass index, m²	0·75 (0·55–0·96)	0·88 (0·59–1·05)	0·79 (0·61–0·91)	0·62 (0·42–0·86)	<0·0001
MNA	24 (22–26)	25 (23–26)	25 (23–26)	23 (21–25)	0·0020
GNRI	115·4 (12·6)	115·9 (12·8)	116·5 (12·1)	113·3 (12·8)	0·46
Medications					
Antidiabetic drugs or insulin					
Insulin	215 (100%)	73 (100%)	82 (100%)	60 (100%)	..
Insulin regimen	..	..	..	..	0·66
Basal	123 (57%)	42 (58%)	44 (54%)	37 (62%)	..
Basal plus prandial	42 (20%)	16 (22%)	18 (22%)	8 (13%)	..
Premixed	50 (23%)	15 (20%)	20 (24%)	15 (25%)	..
Insulin type	..	..	..	..	0·68
Human	127 (59%)	47 (64%)	43 (52%)	37 (62%)	..
Analogue	88 (41%)	26 (36%)	39 (48%)	23 (38%)	..
Gliptin	137 (64%)	42 (58%)	51 (62%)	44 (73%)	0·065
Metformin	137 (64%)	53 (73%)	52 (63%)	32 (53%)	0·021
Sulfonylurea	60 (28%)	20 (27%)	20 (24%)	20 (33%)	0·49
SGLT2 inhibitor	27 (13%)	10 (14%)	14 (17%)	3 (5%)	0·16
GLP-1 receptor antagonist	25 (12%)	9 (12%)	11 (13%)	5 (8%)	0·50
Cardiovascular drugs					
Statin	183 (85%)	64 (88%)	71 (87%)	48 (80%)	0·23
ACE inhibitor or ARB	157 (73%)	52 (71%)	63 (77%)	42 (70%)	0·92
Dihydropyridine CCB	127 (59%)	38 (52%)	50 (61%)	39 (65%)	0·13
Antiplatelet	106 (49%)	30 (41%)	36 (44%)	40 (67%)	0·0043
β blocker	94 (44%)	26 (36%)	36 (44%)	32 (53%)	0·041
Diuretic	42 (20%)	13 (18%)	15 (18%)	14 (23%)	0·44
Aldosterone antagonist	2 (1%)	0	0	2 (3%)	0·055

Data are median (IQR), n (%), or mean (SD). 6MWD=6-min walk distance. ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. CCB=calcium channel blocker. eGFR=estimated glomerular filtration rate. GNRI=Geriatric Nutrition Risk Index. HbA_{1c}=glycated haemoglobin A_{1c}. HK-MoCA=Hong Kong version of the Montreal Cognitive Assessment; IADL=instrumental activities of daily living. MNA=Mini Nutritional Assessment. PASE=Physical Activity Scale for Elderly. SF-12=12-item Short Form Survey. *p values calculated using the Jonckheere-Terpstra test on frailty index tertiles. †Stage 3 or worse. ‡Mild cognitive impairment is indicated by a HK-MoCA score of <22 out of 30.

Table 1: **Baseline characteristics**

Activity Scale for the Elderly (PASE) questionnaire, instrumental activities of daily living, the 12-item Short Form Survey (SF12), 6-min walk distance (6MWD), gait speed, and hand grip dynamometry. Nutrition assessment was done using the full 30-point Mini Nutritional Assessment (MNA), and the Geriatric Nutritional Risk Index (GNRI).[25] All assessments were done at baseline.

Survival ascertainment and analysis

Survival status was ascertained by review of medical records or telephone interview of patients or their family members. All-cause mortality was defined as death from any cause during the follow-up period from the study start date.

Laboratory measurements and blood metabolic profiling

HbA_{1c} in venous blood was measured at Prince of Wales Hospital, Hong Kong. For blood metabolic profiling, serum was centrifuged and extracted from venous blood approximately 2 h after phlebotomy and stored at –80°C. Frozen serum specimens were transported to Nightingale Health (Kuopio, Finland) for ^{1}H-nuclear magnetic resonance (NMR) spectroscopy.[26] 18 metabolites were selected before targeted analysis (metabolites listed in appendix p 12).

Data collection

Before the start of the study, a structured electronic data form was created to collect information on demographics, anthropometric measures, medical co-morbidities, medications, CGM readings, and other data types. The HTML form contained sections and predefined data cells, fields, and selectable boxes designed to maximise consistency and accuracy of data collection. Patients were interviewed in person by a trained research nurse, and all assessments and measurements were performed on the day of device placement before the start of CGM recordings. Patient data and clinical information were checked and queried on the centralised electronic health record system (Clinical Management System) of the Hospital Authority.

Statistical analysis

The sample size calculation was based on power to detect a statistical difference in the survival analysis (appendix p 2). The target sample size was 164, with a two-tailed α 0·05 and β 0·20. Continuous outcomes were summarised as mean (SD), and categorical outcomes as n (%). Depending on the assessment, the cohort was stratified into tertiles for analysis of frailty index, and dichotomised by TIR (≤50% and >50%)[20] or HbA_{1c} (<7·5% and ≥7·5%) as relevant for clinical management.[15] To characterise the relationship between frailty and dysglycaemia, we stratified the cohort at TIR 50%, as guided by the ATTD 2019 consensus

document recommendation for TIR in older or high-risk patients with type 1 or type 2 diabetes[20] (appendix p 4). Unless stated otherwise, frailty index, TIR, and HbA_{1c} were analysed as continuous variables.

For testing the trend across the frailty index tertiles, the Cochran-Armitage test was used to compare categorical variables, whereas the Jonckheere-Terpstra test was used for continuous variables. The Breusch-Pagan test was used to test for heteroscedasticity. The Student's *t* test (for Gaussian variables) and Wilcoxon rank sum test (when the normality assumption was not met) were used to compare continuous outcomes between the TIR groups. Multiple linear regression was used to examine the effects of frailty index, serum albumin level, and HbA_{1c} on the 11 CGM metrics. In regression models, the values of HbA_{1c} and metabolites were $\log_{10}$-transformed for normality. Each model includes adjustment for variables known to influence glucose control in patients with diabetes to varying extents. Depending on the model, adjustment was made for age, sex, eGFR, antidiabetic drugs, insulin type (human or analogue), and multimorbidity.

The Benjamini-Hochberg procedure[27] was used to adjust for multiple hypothesis testing based on a false discovery rate (FDR) of 0·05. The level of significance was determined by the FDR and the corresponding significance ranking of the test such that $P_{(i)} \leq i/n * \text{FDR}$, where i is the ranking of the tested hypothesis among all tested hypotheses ordered by ascending p values; this is the same as $P_{(i)} * n/i \leq \text{FDR}$, where $P_{(i)} * n/i$ is referred to as the adjusted p value. The survival curve for all-cause mortality was computed using the Kaplan-Meier method. Cox proportional hazard modelling was done by regressing metrics of glycaemia on all-cause mortality. A two-tailed $p<0·05$ was considered statistically significant.

For participants who refused to do specific physical tests (gait speed, 6MWD, and hand grip strength), the missing values were imputed using the R package, mice: Multivariate Imputation by Chained Equations.[28] A predictive mean matching model was used to generate ten imputed datasets after 20 iterations. Age, sex, bodyweight, height, HK-MoCA, quality of life measures, systolic and diastolic blood pressure, frailty index, and comorbidities data were used as predictors in the predictive mean matching method. The imputed data were analysed and regression was used to examine if a linear trend was present across the frailty index classes. The pool function in the mice package was used to combine results from the ten imputed sets. The combined results were aggregated using Rubin's rule. All analyses were done using the R statistical programming software package (version 4.1.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Tertiles of frailty index			p value*
	Lowest (n=73)	Middle (n=82)	Uppermost (n=60)	
Mean glucose concentration, mmol/L	8·65 (7·57–10·37)	9·58 (7·94–10·86)	10·14 (8·85–11·94)	0·0005
Glycaemic variability, %CV	33·09% (28·38–39·22)	32·82% (26·65–37·49)	30·76% (25·73–36·83)	0·11
Glucose management indicator†, mmol/mol	53·41 (48·35–61·53)	57·81 (50·09–63·81)	60·43 (54·37–68·91)	0·0005
MAGE, mmol/L	4·78 (3·99–6·43)	5·53 (4·25–6·50)	4·90 (4·08–6·54)	0·63
Level 2 TAR (glucose concentration >13·9 mmol/L)	5·34% (1·48–16·59)	10·91% (2·88–20·69)	12·54 (4·40–28·57)	0·0056
Level 1 TAR (glucose concentration 10·1–13·9 mmol/L)	20·33% (13·44–30·43)	25·54% (15·15–31·24)	26·79% (20·31–36·96)	0·0043
TAR (glucose concentration >10·0 mmol/L)	28·57% (14·85–49·58)	40·86% (24·21–54·64)	48·75% (28·28–68·91)	0·0006
TIR (glucose concentration 3·9–10·0 mmol/L)	68·73% (48·12–79·57)	55·05% (43·83–70·03)	51·25% (31·09–67·33)	0·0010
TBR (glucose concentration <3·9 mmol/L)	1·33% (0·00–4·64)	0·47% (0·00–3·29)	0·00% (0·00–1·23)	0·017
Level 1 TBR (glucose concentration 3·0–3·8 mmol/L)	1·01% (0·00–3·92)	0·30% (0·00–1·92)	0·00% (0·00–1·03)	0·013
Level 2 TBR (glucose concentration <3·0 mmol/L)	0·00% (0·00–0·42)	0·00% (0·00–0·35)	0·00% (0·00–0·00)	0·18

Data are median (IQR). %CV=coefficient of glycaemic variability. CGM=continuous glucose monitor. MAGE=mean amplitude of glucose excursion. TAR=time above range. TBR=time below range. TIR=time in range. *p values were calculated using the Jonckheere-Terpstra test on frailty index tertiles. †Glucose management indicator (mmol/mol) = 12·71 + 4·70587 × (mean glucose in mmol/L).[19]

Table 2: **Comparison of CGM metrics across tertiles of the frailty index**

Results

Between July 25, 2018, and Sept 27, 2019, 225 participants were recruited, 222 of whom had CGMs fitted. Three individuals withdrew from the study, two due to end-stage kidney disease and one due to an absence of insulin requirement before CGM placement. In addition, seven participants did not return CGMs or returned CGMs with irretrievable data (appendix p 3). 215 participants (median age 74 years [IQR 71–78]) had analysable data (table 1), 190 (88%) of whom were classified as frail and 25 (12%) of whom were classified as non-frail (appendix p 5). For participants who refused to do specific physical tests (gait speed, n=24; 6MWD, n=33; hand grip strength, n=5), the missing values were imputed. The fraction of missing information was 0·0902 for gait speed, 0·0193 for 6MWD, and 0·0219 for hand grip strength; the proportion of total variance due to missingness (λ) was 0·0797 for gait speed, 0·0179 for 6MWD, and 0·0125 for hand grip strength.

Older age, greater HbA_{1c}, lower eGFR, stroke, adverse global frailty measures, and cognitive decline assessed by HK-MoCA were all significantly associated with increased frailty (table 1).

28 608 h (mean 5·54 days [SD 1·67] per person) of CGM recordings were compiled. The mean number of fingerstick calibrations per participant within the study

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value
Mean glucose concentration	7·67 (4·43 to 10·92)	<0·0001	7·67 (4·40 to 10·93)	<0·0001	8·12 (4·82 to 11·42)	<0·0001	7·78 (4·30 to 11·25)	<0·0001	7·86 (4·37 to 11·35)	<0·0001	8·31 (4·79 to 11·83)	<0·0001
Glycaemic variability	−14·47 (−25·22 to −3·72)	0·0086	−13·65 (−24·41 to −2·88)	0·013	−13·60 (−24·60 to −2·60)	0·016	−13·72 (−25·19 to −2·25)	0·019	−13·02 (−24·52 to −1·52)	0·027	−12·82 (−24·55 to −1·09)	0·032
Glucose management indicator	36·10 (20·83 to 51·38)	<0·0001	36·08 (20·70 to 51·46)	<0·0001	38·21 (22·70 to 53·73)	<0·0001	36·59 (20·26 to 52·93)	<0·0001	37·00 (20·57 to 53·43)	<0·0001	39·11 (22·55 to 55·67)	<0·0001
MAGE	−0·10 (−2·88 to 2·69)	0·95	0·07 (−2·73 to 2·87)	0·96	0·24 (−2·62 to 3·11)	0·87	0·42 (−2·55 to 3·39)	0·78	0·59 (−2·40 to 3·57)	0·70	0·73 (−2·33 to 3·79)	0·64
Level 2 TAR (glucose concentration >13·9 mmol/L)	51·72 (27·97 to 75·48)	<0·0001	52·47 (28·59 to 76·36)	<0·0001	55·72 (31·71 to 79·72)	<0·0001	51·04 (25·56 to 76·52)	0·0001	52·41 (26·85 to 77·97)	<0·0001	55·88 (30·23 to 81·52)	<0·0001
Level 1 TAR (glucose concentration 10·1–13·9 mmol/L)	19·44 (3·09 to 35·79)	0·020	18·51 (2·11 to 34·92)	0·027	19·32 (2·62 to 36·01)	0·024	18·50 (1·91 to 35·09)	0·029	17·97 (1·30 to 34·65)	0·035	18·34 (1·46 to 35·23)	0·033
TAR (glucose concentration >10·0 mmol/L)	71·17 (40·34 to 102·00)	<0·0001	70·99 (39·95 to 102·02)	<0·0001	75·03 (43·75 to 106·31)	<0·0001	69·54 (37·05 to 102·04)	<0·0001	70·39 (37·71 to 103·07)	<0·0001	74·22 (41·35 to 107·09)	<0·0001
TIR (glucose concentration 3·9–10·0 mmol/L)	−66·30 (−95·90 to −36·70)	<0·0001	−66·93 (−96·72 to −37·14)	<0·0001	−70·29 (−100·34 to −40·24)	<0·0001	−65·16 (−96·50 to −33·81)	<0·0001	−66·63 (−98·09 to −35·17)	<0·0001	−70·17 (−101·87 to −38·47)	<0·0001
TBR (glucose concentration <3·9 mmol/L)	−4·87 (−12·67 to 2·93)	0·22	−4·06 (−11·82 to 3·71)	0·30	−4·74 (−12·59 to 3·11)	0·24	−4·39 (−12·67 to 3·89)	0·30	−3·76 (−12·04 to 4·52)	0·37	−4·05 (−12·39 to 4·28)	0·34
Level 1 TBR (glucose concentration 3·0–3·8 mmol/L)	−4·33 (−7·74 to −0·92)	0·013	−3·99 (−7·39 to −0·59)	0·022	−4·13 (−7·60 to −0·66)	0·020	−4·00 (−7·67 to −0·34)	0·032	−3·71 (−7·37 to −0·05)	0·047	−3·80 (−7·53 to −0·07)	0·046
Level 2 TBR (glucose concentration <3·0 mmol/L)	−0·54 (−6·01 to 4·94)	0·85	−0·07 (−5·54 to 5·40)	0·98	−0·61 (−6·12 to 4·90)	0·83	−0·38 (−6·16 to 5·39)	0·90	0·05 (−5·84 to 5·75)	0·99	−0·26 (−6·06 to 5·55)	0·93

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, and eGFR. Model 3: adjusted for age, sex, eGFR, antidiabetic drugs*, and insulin type (human or analogue). Model 4: adjusted for age, sex, and multimorbidity†. Model 5: adjusted for age, sex, multimorbidity, and eGFR. Model 6: adjusted for age, sex, multimorbidity, eGFR, antidiabetic drugs*, and insulin type (human or analogue). The β coefficient represents a modelled increase in the CGM metric as the frailty index increases by one deficit. As the frailty index is a ratio of the actual number of deficits to the total inventory of deficits, a 1-unit increase in deficit corresponds to a 0·025 (1/40) increase in the frailty index. For example, in model 1 the results suggested that with each 1-unit increase in the frailty index, the mean glucose concentration increased by 7·67 mmol/L, or with one additional deficit (ie, an increase of 0·025 in the frailty index), the mean glucose concentration increased by 0·19 mmol/L (7·67/40). CGM=continuous glucose monitor. eGFR=estimated glomerular filtration rate. MAGE=mean amplitude of glucose excursion. TAR=time above range. TBR=time below range. TIR=time in range. *Antidiabetic drugs refer to gliptin, metformin, sulfonylurea, SGLT2 inhibitors, and GLP-1 receptor agonists that were each treated as an individual variable in the regression model. †Multimorbidity refers to hypertension, cancer, chronic lung disease, myocardial infarction, atrial fibrillation or atrial flutter, heart failure, stroke, and coronary artery disease that were each included as an individual variable in the regression model.

Table 3: **Regression modelling of the effect of frailty index as a continuous independent variable on CGM metrics**

	HbA_{1c} model 1		HbA_{1c} model 2		HbA_{1c} model 3		Serum albumin model 1		Serum albumin model 2		Serum albumin model 3	
	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value
Patients with HbA_{1c} <7·5% (n=56)												
Mean glucose concentration	10·04 (−4·74 to 24·82)	0·18	9·65 (−7·16 to 26·45)	0·25	9·75 (−9·11 to 28·61)	0·30	−4·07 (−11·15 to 3·01)	0·25	5·08 (−13·02 to 2·86)	0·20	−6·02 (−15·43 to 3·40)	0·20
Glycaemic variability	89·25 (4·29 to 174·21)	0·040	56·94 (−33·37 to 147·26)	0·21	42·34 (−55·89 to 140·56)	0·39	12·85 (−29·23 to 54·92)	0·54	9·50 (−34·01 to 53·00)	0·66	−15·04 (−64·70 to 34·62)	0·54
Glucose management indicator	47·24 (−22·33 to 116·80)	0·18	45·40 (−33·69 to 124·48)	0·25	45·89 (−42·88 to 134·65)	0·30	−19·16 (−52·48 to 14·17)	0·25	−23·91 (−61·28 to 13·45)	0·20	−28·32 (−72·63 to 15·99)	0·20
MAGE	21·33 (8·34 to 34·33)	0·0018	17·83 (3·47 to 32·18)	0·016	14·41 (−1·98 to 30·81)	0·083	−1·76 (−8·59 to 5·06)	0·61	−3·14 (−10·31 to 4·03)	0·38	−6·38 (−14·68 to 1·91)	0·13
Level 2 TAR (glucose concentration >13·9 mmol/L)	85·18 (−6·83 to 177·19)	0·068	78·06 (−25·73 to 181·84)	0·14	78·56 (−35·54 to 192·66)	0·17	−32·39 (−76·78 to 12·01)	0·15	−39·17 (−88·23 to 9·88)	0·11	−63·53 (−118·48 to −8·59)	0·025
Level 1 TAR (glucose concentration 10·1–13·9 mmol/L)	33·51 (−76·60 to 143·63)	0·54	20·26 (−102·12 to 142·64)	0·74	10·24 (−128·40 to 148·87)	0·88	−19·46 (−71·85 to 32·94)	0·46	−2·17 (−79·87 to 35·54)	0·44	−16·99 (−86·51 to 52·53)	0·62
TAR (glucose concentration >10·0 mmol/L)	118·70 (−55·52 to 292·91)	0·18	98·32 (−98·00 to 294·64)	0·32	88·80 (−133·46 to 311·05)	0·42	−51·84 (−135·13 to 31·44)	0·22	−61·34 (−153·63 to 30·95)	0·19	−80·53 (−190·06 to 29·01)	0·14
TIR (glucose concentration 3·9–10·0 mmol/L)	−149·51 (−321·79 to 22·76)	0·087	−113·86 (−306·32 to 78·60)	0·24	−105·35 (−326·25 to 115·56)	0·34	60·70 (−22·09 to 143·48)	0·15	74·03 (−15·92 to 163·97)	0·10	107·09 (0·40 to 213·79)	0·049
TBR (glucose concentration <3·9 mmol/L)	30·82 (−22·13 to 83·76)	0·25	15·54 (−42·55 to 73·64)	0·59	16·55 (−47·94 to 81·04)	0·61	−8·85 (−34·30 to 16·60)	0·49	−12·69 (−40·05 to 14·68)	0·36	−26·57 (−57·90 to 4·76)	0·094
Level 1 TBR (glucose concentration 3·0–3·8 mmol/L)	9·40 (−21·76 to 40·56)	0·55	2·59 (−31·62 to 36·79)	0·88	−0·52 (−39·07 to 38·04)	0·98	−4·51 (−19·36 to 10·35)	0·55	−5·66 (−21·79 to 10·47)	0·48	−14·46 (−33·24 to 4·33)	0·13
Level 2 TBR (glucose concentration <3·0 mmol/L)	21·42 (−9·00 to 51·84)	0·16	12·96 (−20·62 to 46·53)	0·44	17·07 (−21·29 to 55·42)	0·37	−4·34 (−19·08 to 10·39)	0·56	−7·03 (−22·91 to 8·86)	0·38	−12·11 (−31·19 to 6·97)	0·21

(Table 4 continues on next page)

	HbA_{1c} model 1		HbA_{1c} model 2		HbA_{1c} model 3		Serum albumin model 1		Serum albumin model 2		Serum albumin model 3	
	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value
(Continued from previous page)												
Patients with HbA_{1c} ≥7·5% (n=159)												
Mean glucose concentration	21·16 (14·61 to 27·70)	<0·0001	22·02 (15·15 to 28·89)	<0·0001	21·23 (14·09 to 28·37)	<0·0001	−11·82 (−18·79 to −4·85)	0·0010	−11·32 (−18·69 to −3·96)	0·0028	−12·54 (−20·07 to −5·00)	0·0013
Glycaemic variability	−15·38 (−37·74 to 6·98)	0·18	−14·27 (−37·72 to 9·18)	0·23	−15·09 (−39·71 to 9·54)	0·23	0·37 (−21·70 to 22·43)	0·97	−2·95 (−26·00 to 20·11)	0·80	−3·43 (−27·69 to 20·83)	0·78
Glucose management indicator	99·56 (68·77 to 130·35)	<0·0001	103·62 (71·29 to 135·96)	<0·0001	99·90 (66·28 to 133·52)	<0·0001	−55·61 (−88·41 to −22·82)	0·0010	−53·29 (−87·94 to −18·64)	0·0028	−58·99 (−94·46 to −23·52)	0·0013
MAGE	4·01 (−2·16 to 10·18)	0·20	6·23 (−0·38 to 12·84)	0·064	5·49 (−1·38 to 12·36)	0·12	−3·83 (−9·67 to 2·02)	0·20	−4·60 (−10·67 to 1·48)	0·14	−5·00 (−11·37 to 1·37)	0·12
Level 2 TAR (glucose concentration >13·9 mmol/L)	159·96 (109·70 to 210·21)	<0·0001	165·39 (112·47 to 218·32)	<0·0001	158·37 (103·65 to 213·09)	<0·0001	−82·58 (−136·20 to −28·96)	0·0027	−82·80 (−139·28 to −26·32)	0·0043	−93·35 (−150·79 to −35·90)	0·0016
Level 1 TAR (glucose concentration 10·1–13·9 mmol/L)	30·67 (−3·35 to 64·69)	0·077	27·70 (−5·87 to 61·27)	0·11	25·98 (−8·90 to 60·86)	0·14	−18·38 (−51·95 to 15·18)	0·28	−6·47 (−39·57 to 26·63)	0·70	−3·00 (−37·42 to 31·42)	0·86
TAR (glucose concentration >10·0 mmol/L)	190·63 (130·52 to 250·73)	<0·0001	193·09 (130·79 to 255·40)	<0·0001	184·35 (120·03 to 248·67)	<0·0001	−100·96 (−164·96 to −36·97)	0·0022	−89·27 (−155·94 to −22·60)	0·0090	−96·34 (−164·30 to −28·39)	0·0058
TIR (glucose concentration 3·9–10·0 mmol/L)	−183·31 (−240·88 to −125·75)	<0·0001	−186·46 (−246·32 to −126·60)	<0·0001	−180·39 (−242·39 to −118·40)	<0·0001	102·24 (41·12 to 163·36)	0·0012	92·98 (29·12 to 156·84)	0·0046	101·28 (35·93 to 166·64)	0·0026
TBR (glucose concentration <3·9 mmol/L)	−7·31 (−24·10 to 9·47)	0·39	−6·63 (−24·03 to 10·76)	0·45	−3·96 (−21·81 to 13·90)	0·66	−1·28 (−17·77 to 15·21)	0·88	−3·70 (−20·73 to 13·32)	0·67	−4·94 (−22·42 to 12·54)	0·58
Level 1 TBR (glucose concentration 3·0–3·8 mmol/L)	−4·52 (−10·82 to 1·78)	0·16	−4·01 (−10·65 to 2·63)	0·23	−3·45 (−10·39 to 3·49)	0·33	2·91 (−3·28 to 9·11)	0·35	1·86 (−4·65 to 8·38)	0·57	1·77 (−5·05 to 8·58)	0·61
Level 2 TBR (glucose concentration <3·0 mmol/L)	−2·80 (−15·29 to 9·70)	0·66	−2·62 (−15·45 to 10·20)	0·69	−0·51 (−13·57 to 12·56)	0·94	−4·19 (−16·43 to 8·04)	0·50	−5·57 (−18·08 to 6·95)	0·38	−6·71 (−19·46 to 6·04)	0·30

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, and multimorbidity*. Model 3: adjusted for age, sex, multimorbidity*, eGFR, antidiabetic drugs†, and insulin type (human or analogue). CGM=continuous glucose monitor. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin A_{1c}. MAGE=mean amplitude of glucose excursion. TAR=time above range. TBR=time below range. TIR=time in range. *Multimorbidity refers to hypertension, cancer, chronic lung disease, myocardial infarction, atrial fibrillation or atrial flutter, heart failure, stroke, and coronary artery disease that were each included as an individual variable in the regression model. †Antidiabetic drugs refer to gliptin, metformin, sulfonylurea, SGLT2 inhibitors, and GLP-1 receptor agonists that were each treated as an individual variable in the regression model.

Table 4: **Adjusted regression modelling of the effect of HbA_{1c} and serum albumin on CGM metrics stratified by HbA_{1c} less than 7·5% versus HbA_{1c} 7·5% or more**

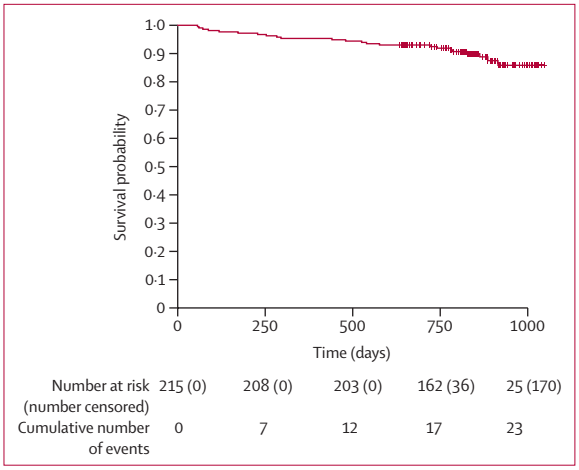

Figure: **Kaplan-Meier estimate of overall survival**

period was 14·6 (SD 6·66). After Benjamini-Hochberg correction for multiple testing, eight of 11 CGM metrics were significantly associated with frailty (table 2). Adjusted multiple regression identified eight of 11 metrics including mean glucose concentration, glucose management indicator, and all TAR metrics[20] as being positively correlated with frailty, whereas TIR (glucose concentration 3·9–10·0 mmol/L) was inversely correlated with frailty (table 3). An inter-relationship between the metrics is suggested by a positive correlation between TBR and TIR (r=0·277, p<0·0001), and negative correlation between TBR and TAR (r=–0·226, p<0·0001). Overall, TAR metrics were as strongly associated with increased HbA_{1c} (appendix p 6) as they were with increasing frailty (table 2), whereas the associations between frailty and TBR metrics were variable or absent (tables 2, 3).

When the cohort was stratified by TIR, we found that patients with reduced glucose control indicated by a TIR of 50% or less (ie, dysglycaemia) were older (median age 76 years [IQR 71–79] *vs* 73 years [71–77]; p=0·039), and had greater median HbA_{1c} (8·9% [IQR 8·1–10·0] *vs* 7·8% [7·1–8·6]; p<0·0001) than those with a TIR of more than 50% (euglycaemia; appendix p 7). The subgroup of patients with dysglycaemia included individuals who were more frail (median frailty index 0·23 [IQR 0·17–0·30] *vs* 0·18 [0·13–0·25]; p=0·0045), with lower median PASE scores (26 [IQR 5–57] *vs* 55 [28–73]; p=0·0003), shorter median 6MWD (251 m [IQR 152–309] *vs* 298 m [225–344]; p=0·0043), and slightly poorer nutrition (median MNA score 24 [IQR 22–25] *vs* 24 [23–26]; p=0·029), compared with the subgroup with euglycaemia (appendix p 7).

There were no significant associations between insulin regimen (basal, basal plus prandial, or premixed), insulin type (human or analogue), or antidiabetic drugs and frailty and hyperglycaemia or dysglycaemia when individually assessed as independent variables in regression analysis (appendix pp 8–9). Interaction testing of glucose-lowering agents identified only three (2%) of 165 pairs with statistically significant interactions (appendix pp 10–11).

	Model 1		Model 2		Model 3	
	HR (95% CI)	p value	Adjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Mean glucose concentration	1·157 (1·011–1·324)	0·034	1·144 (0·998–1·313)	0·054	1·112 (0·958–1·291)	0·16
Glycaemic variability	0·994 (0·945–1·045)	0·81	0·991 (0·941–1·044)	0·75	0·999 (0·949–1·052)	0·96
Glucose management indicator	1·032 (1·002–1·062)	0·034	1·029 (1·000–1·060)	0·054	1·023 (0·991–1·056)	0·16
MAGE	1·026 (0·854–1·234)	0·78	1·032 (0·850–1·252)	0·75	1·035 (0·856–1·251)	0·72
Level 2 TAR (glucose concentration >13·9 mmol/L)	1·021 (1·004–1·038)	0·014	1·019 (1·002–1·037)	0·027	1·016 (0·997–1·035)	0·10
Level 1 TAR (glucose concentration 10·1–13·9 mmol/L)	0·995 (0·963–1·029)	0·78	0·992 (0·959–1·026)	0·63	0·986 (0·953–1·020)	0·42
TAR (glucose concentration >10·0 mmol/L)	1·014 (0·998–1·030)	0·094	1·012 (0·990–1·029)	0·15	1·008 (0·990–1·026)	0·37
TIR (glucose concentration 3·9–10·0 mmol/L)	0·984 (0·968–1·001)	0·064	0·986 (0·969–1·003)	0·11	0·990 (0·972–1·009)	0·29
TBR (glucose concentration <3·9 mmol/L)	1·012 (0·957–1·071)	0·67	1·009 (0·951–1·071)	0·76	1·013 (0·958–1·071)	0·64
Level 1 TBR (glucose concentration 3·0-3·8 mmol/L)	1·039 (0·905–1·192)	0·59	1·027 (0·898–1·173)	0·70	1·056 (0·921–1·211)	0·44
Level 2 TBR (glucose concentration <3·0 mmol/L)	1·011 (0·930–1·098)	0·80	1·008 (0·924–1·100)	0·86	1·008 (0·922–1·101)	0·87
HbA_{1c}	1·172 (0·889–1·544)	0·26	1·138 (0·861–1·502)	0·36	1·086 (0·819–1·440)	0·57

Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, and frailty index. CGM=continuous glucose monitor. HbA_{1c}=glycated haemoglobin A_{1c}. HR=hazard ratio. MAGE=mean amplitude of glucose excursion. TAR=time above range. TBR=time below range. TIR=time in range.

Table 5: **Cox proportional hazard modelling of the effect of CGM metrics and HbA_{1c} as independent variables on all-cause mortality**

To explore circulating factors associated with frailty in older adults with type 2 diabetes, we assayed 18 metabolites and low-molecular-weight proteins, and identified albumin, creatinine, glutamine, and glycine as being associated with frailty index tertile (appendix p 12). We obtained blood samples from all participants and were able to perform metabolic analysis on all samples. Serum albumin was inversely correlated with mean glucose concentration, glucose management indicator, and TAR (overall TAR and level 2 TAR), and positively correlated with TIR (appendix p 13), whereas glutamine and glycine were initially identified as potential candidates (appendix p 12) but were not subsequently correlated with any CGM metric (appendix pp 14–15). When the data were dichotomised at HbA_{1c} 7·5%, a clinically important threshold for diabetes management, the majority of CGM metrics for hyperglycaemia or

dysglycaemia in the group with HbA_{1c} of 7·5% or more remained significantly correlated with HbA_{1c} and serum albumin concentrations (table 4; see appendix p 6 for unstratified HbA_{1c} analysis).

To determine if CGM metrics were significant predictors of mortality, participants in the study cohort were followed up for approximately 3 years, from July 25, 2018, to June 24, 2021. During a median follow-up of 28·0 months (IQR 25·3–30·4), 23 (11%) of 215 individuals died (figure). Cox regression adjusted for age and sex determined that level 2 TAR was the only significant predictor of all-cause mortality (p=0·028), where each 1% increment of level 2 TAR was associated with an increased mortality hazard of 1·9% (model 2; table 5). Further analysis identified frailty as an explanatory factor for the level 2 TAR-associated mortality hazard (model 3; table 5), and no interaction between level 2 TAR and frailty in the estimate of mortality hazard (appendix p 16). The proportional hazards assumption was met for all models using the Schoenfeld test (appendix p 17).

Discussion

To our knowledge, this study is the first CGM characterisation of glucose control in association with comprehensive assessment of frailty, comorbidities, and antidiabetic and cardiovascular drug effects in a cohort of predominantly frail older adults with type 2 diabetes on insulin therapy. The clinical phenotype profiled in our global frailty assessment tracked well with the frailty index from the lowest to uppermost tertile that corresponded to worsening physical, neurocognitive, sociobehavioural, and nutritional domains of frailty. Individuals in the uppermost tertile of the frailty index showed evidence of at least mild cognitive impairment (ie, below the threshold of <22 out of 30 in HK-MoCA[24]), reduced functional independence, and decreased physical activity and motor function.

We originally hypothesised that increasing frailty would be associated with a greater proportion of patients with TBR; but instead, we observed that patients with a greater frailty index had a lower TBR and a higher TAR. Of note, we identified level 2 TAR to be positively correlated with frailty and future mortality, and further testing did not show a significant interaction between level 2 TAR and frailty index. These findings suggest that level 2 TAR is a clinically actionable and prognostic marker in the management of frail older adults with type 2 diabetes.

Clinical society guidelines and standard of care documents provide recommendations for glucose control in different individuals, depending on disease and patient type (eg, type 1 diabetes, type 2 diabetes, older patients, or patients at high risk of diabetic complications),[20] health status (good health [group 1], intermediate health [group 2], poor health [group 3]),[14] patient characteristics,[15] and co-morbidities.[3] Although an individualised approach to diabetes management and prevention of hypoglycaemia is universally advised for older patients with complex comorbidities, the means of meeting the recommended clinical targets are unguided. Our findings add to the current literature by suggesting that increased proportion of time in severe hyperglycaemia (ie, level 2 TAR) is associated with adverse outcomes in this patient population. As chronic hyperglycaemia can worsen frailty,[7] an ageing-related syndrome associated with increased adverse outcomes and mortality,[3–6] the findings of our study suggest that level 2 TAR should be curtailed, particularly when HbA_{1c} is 7·5% or more, while maintaining the guideline-recommended TIR and TBR targets. That each percentage point above level 2 TAR was associated with increased mortality hazard further supports monitoring of this CGM metric in older adults who are frail. Future clinical trials are needed to identify and compare therapeutic agents or combinations of agents that allow the level 2 TAR target to be met without compromising TBR and TIR.

In older patients with type 2 diabetes, the ATTD 2019 International Consensus document recommended: (1) TIR more than 50% or more than 12 h/day with a target glucose concentration range of 3·9–10·0 mmol/L (70–180 mg/dL); (2) TBR (glucose concentration <3·9 mmol/L or <70 mg/dL) less than 1% or less than 15 min/day; (3) level 1 TAR (glucose concentration >10·1–13·9 mmol/L or 182–250 mg/dL) less than 50% or less than 12 h/day; and (4) level 2 TAR (glucose concentration >13·9 mmol/L or >250 mg/dL) less than 10% or less than 2 h 24 min/day (appendix p 4).[20] Compared with the majority of younger adults with type 2 diabetes whose recommended level 2 TAR target was less than 5%, the target of less than 10% for older adults with type 2 diabetes could potentially be associated with hazards. Unless severe hypoglycaemic (glucose concentration <3·0 mmol/L) episodes are demonstrable and frequent, it might be prudent to reserve the upward adjusted level 2 TAR target of less than 10% for specific patients after assessing CGM results and benefit-to-risk ratio. Our cohort mostly met the ATTD 2019 guideline-recommended TIR, TAR, and level 1 TAR targets (appendix p 4), whereas the level 2 TAR target was exceeded in the middle and uppermost frailty tertiles, and the overall TBR target was exceeded in the lowest frailty tertile, suggesting a need for alternative strategies to improve targeting of TBR and level 2 TAR. It is noteworthy that as TIR decreased and TAR increased with incremental frailty, TBR and level 1 TBR (glucose concentrations 3·0–3·8 mmol/L) both decreased with increasing frailty, whereas level 2 TBR (glucose concentration <3·0 mmol/L) did not vary between frailty index tertiles. Although the association between TBR metrics and frailty was weak (for level 1 TBR) or absent (for level 2 TBR), the overall trend suggested an inverse relationship between frailty and TBR. This complex inter-relationship is statistically supported by a positive correlation between TBR and TIR, and negative correlation between TBR and TAR. Insulin type, insulin regimen, and antidiabetic drugs had no

significant effect on glycaemic control (appendix pp 8–9); it might be inferred that further reduction of glucose control at the expense of TIR and TAR might not necessarily reduce hypoglycaemic episodes in older patients. Based on our findings, it might be prudent to perform CGM and frailty assessment before committing an older adult with type 2 diabetes to a less restrictive glucose control strategy.

Our findings differ from those previously reported in older adults with type 1 diabetes.[16,18] In patients with type 1 diabetes, glucose management indicator and glycaemic variability were indicative of high risk for hypoglycaemia, whereas in patients with type 2 diabetes, glycaemic variability was uninformative, and glucose management indicator was correlated with incremental frailty, metrics of hyperglycaemia (not hypoglycaemia), and HbA_{1c} and albumin when HbA_{1c} was 7·5% or more.

In targeted metabolic profiling, we identified an association between reduced serum albumin concentration and increasing frailty in relation to reduced glycaemic control or TIR. This association could be partially explained by chronic kidney disease, which variably impacts renal clearance of insulin as well as the pharmacokinetics of administered insulin. Circulating and tissue-associated albumin might also have context-dependent physiological functionalities that buffer the different metabolic and glycaemic effects of insulin.[29] Using the same ^{1}H-NMR metabolic profiling technology as in our study, a northern European population-based study of more than 17 000 individuals from Estonian Biobank and FINRISK found reduced blood albumin concentrations to be predictive of cardiovascular and non-cardiovascular deaths.[30] Those findings corroborated an earlier study of more than 4000 older adults from the USA that showed that low blood albumin concentrations independently predicted all-cause mortality and were inversely associated with increasing disability level, and prompted the authors to propose the combined measure of albumin and disability as a gauge of frailty.[31]

Our study has several limitations. First, our study was designed to recruit predominantly frail older adults with type 2 diabetes who were on insulin therapy. It is noteworthy that the majority had mild-to-moderate frailty (appendix p 5). The challenges of recruiting severely frail older adults might be circumvented by including inpatients or those residing in long-term care facilities. Generalisability and external validation beyond Hong Kong are needed. Second, the ATTD 2019 consensus recommended the use of 14-day CGM for clinical practice, whereas the iPro2 CGM used in this study provided week-long recording. Although it is possible that a longer duration of recording might improve data precision, professional or masked CGMs with longer sensor life were not available at the time of study inception. The iPro2 has the advantage of providing masked CGM data without introducing bias. Third, although CGM detection of severe hypoglycaemia can have error rates of 10–15% according to manufacturers and depending on the device, a study analysing more than 5000 paired glucose values found that the performance of iPro2 and another commonly used CGM (FreeStyle Libre Pro) were generally closely correlated (r=0·96, p<0·01).[32] The clinical benefits of CGM in patients with type 1 diabetes[17] should encourage its use for individualised diabetes management. Fourth, although we have individually adjusted for the effects of each antidiabetic drug, including metformin, in regression modelling and found no significant effects from drugs, we cannot exclude the possibility of reduced metformin use having an influence on glucose control. Although metformin use is contraindicated in patients with advanced chronic kidney disease, our study's predefined exclusion criteria of eGFR less than 15 mL/min per 1·73 m² and terminal illness might have reduced potential bias and skewing. Finally, although malnutrition could be a potential cause of reduced serum albumin concentrations, our findings from nutrition assessment using MNA and GNRI are inconclusive.

In summary, frailty and dysglycaemia in patients with diabetes remain poorly understood.[3] Although avoidance of severe hypoglycaemia in older adults who require insulin therapy remains an important goal of diabetes management, future efforts might be directed at curtailing TAR (particularly level 2 TAR) and maintaining TIR with the guidance of CGM, and innovating alternative strategies to improve frailty and adverse outcomes.

Contributors

EF, TK, and RCWM conceptualised and designed the study. EF obtained research funding. EF, L-TL, and WBG developed the statistical analysis plan. L-TL and LH did the formal statistical analysis. EF, L-TL, EC, and TK performed the literature search, and critically reviewed the methodology with KFC, JSWL, EH, WYS, RCWM, and EC. JJYS provided oversight and resource support. EF and KFC administered the project. EF, KFC, GHWL, YTC, BNA, and SX contributed to data collection. EF, L-TL, LH, JSWL, IK, RCWM, QC, M-RJ, EC, and TK contributed to data analysis and interpretation. EF and L-TL wrote the first draft of the manuscript. EF, TK, JSWL, EH, WYS, JJYS, IK, WBG, QC, M-RJ, RCWM, and EC contributed to revision and editing. All authors had access to the data reported in this study. All authors had the opportunity to review the manuscript prior to submission. All authors had the final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Data collected for this study, including de-identified individual participant data and a data dictionary defining each field in the set, are available for research. Queries should be directed to the corresponding author at: e.fung@cuhk.edu.hk. Access to the data will be available 12 months after the date of publication of this manuscript. The interested investigator should submit a brief one-page study proposal and complete a data access and transfer agreement facilitated by the Office of Research and Knowledge Transfer Services, The Chinese University of Hong Kong (https://www.orkts.cuhk.edu.hk/).

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