**Biochemical estimation of muscle mass and unbiased assessment of kidney function using serum creatinine and cystatin-C: A prognostic validation study within UK Biobank**

**Statistical Analysis Plan**

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**Background**

Sarcopenia, loss of muscle mass, is a major complication for patients admitted to hospital and intensive care. Multimorbidity; the presence of two or more long-term conditions, is associated with the presence of sarcopenia (1).

Sarcopenia Index (SI) (creatinine:cystatin-C x100) is shown to correlate with loss of muscle mass and predict hospital mortality in different cohorts of patients (2, 3, 4, 5). Kidney disease is associated with cardiovascular disease and is an emerging contributor to multimorbidity (6). Interventions for preventing sarcopenia, kidney disease and cardiovascular disease currently exist.

Kidney disease is classified using estimated glomerular filtration rate (eGFR) by using serum creatinine in the CKD-EPI formula. Skeletal muscle generates a significant proportion of creatinine, introducing bias during states of fluctuating muscle mass such as during acute illness. Falsely reduced creatinine due to sarcopenia causes inaccuracies and delays in identifying and preventing kidney disease related to critical illness. Cystatin-C is a glomerular filtration biomarker unaffected by muscle mass and can calculate eGFR. It is recommended in settings where creatinine may be unreliable, for example, in critical illness and sarcopenia.

We propose three workstreams; firstly, we will validate the sarcopenia index using MRI measured muscle quantity. We will then investigate the relationship between sarcopenia index, mortality, and the development of multimorbidity. Lastly, we will investigate the relationship between sarcopenia index (a surrogate of muscle quantity) and the assessment of kidney function using cystatin-C, and the effect that this has on outcomes.

This will lead to a refined assessment of both sarcopenia and kidney function in patients with acute and chronic illnesses. The prediction and early intervention of these conditions will positively impact on multimorbidity and its interaction with acute and critical illness.

**Workstream 1: Validation of Sarcopenia Index using MRI calculated muscle quantity and measures of muscle function**

**Background**

Sarcopenia has been identified as an important risk factor for morbidity and mortality in the general population (7). Traditionally, Sarcopenia described the loss of muscle quantity in the ageing population (8). However, it is increasingly becoming recognised as a clinical syndrome affecting multi-morbid patients and not just the older population (9).

The European Working Group on Sarcopenia in Older People (EWGSOP) revised their definition of sarcopenia in 2018 to include low muscle strength and low physical performance, as well as low muscle quantity (10). Low muscle strength and physical performances have been independently associated with increased morbidity and mortality (11, 12, 13). The EWGSOP advise that sarcopenia should be suspected in those with low muscle strength, confirmed in those with additional low muscle quantity or quality and is severe in those with low strength, quantity, and physical performance.

A systematic review has identified that critical care patients are at risk of losing 2% of their muscle mass per day during the first week of critical illness (14). The gold standard for measuring muscle quantity is imaging based techniques with CT and MRI. Dual energy x-ray absorptiometry (DEXA) and bioelectrical impedance analysis of body composition have also been developed to estimate lean muscle mass (15). The practicalities and resources required for this in critical care patients mean that there is not an easily accessible tool to assess sarcopenia in all patients.

A biochemical marker, Sarcopenia Index (SI, creatinine:cystatin-Cx100), has been validated in critical care (2, 3) and lung transplant (4) patients using CT surface area as an estimate of muscle quantity. Kashani et al. also demonstrated the association of SI with adverse outcomes from critical illness (2).

We aim to validate the SI in the UK Biobank cohort using MRI measured muscle quantity. The relationship between SI and muscle quantity will also be explored using bioelectrical impedance analysis (BIA). We will further investigate the ability of SI to identify low muscle strength, as measured by grip strength, and physical performance, as measured by walking pace. These findings will add strength to the use of the SI as a biochemical estimation of muscle quantity, a surrogate marker for sarcopenia and poor health care outcomes.

**Study Objectives**

***Primary research question***

Does sarcopenia index correlate with MRI measures of muscle quantity?

***Secondary research question***

Does sarcopenia index correlate with measures of muscle function?

***Primary outcome measure***

SI correlation with muscle quantity measured by MRI

* Muscle quantity will be measured using thigh fat free muscle volume (FFMV)

***Secondary outcome measures***

SI correlation with muscle quantity measured by bioelectrical impedance analysis (BIA)

* Muscle quantity will be measured using appendicular fat free mass and converted to appendicular lean mass (ALM), detailed below

SI correlation with muscle function

* Hand-grip strength
* Self-reported walking pace

***Exploratory analysis***

SI correlation with muscle quality measured by MRI

* Muscle quality will be measured using muscle fat infiltration (MFI) fraction

**Study population**

We will perform a cross-sectional study to investigate our objectives.

***Data source***

The data analysis will be carried out using a cohort of patients from the UK Biobank database that have had abdominal MRI imaging. 500,000 participants aged 40-69 years old were recruited during 2006-2010 from the United Kingdom. A full assessment was performed at the recruitment visit including health questionnaires, measurements, and blood sample collection (16). 100,000 participants were invited for MRI imaging during 2014 and the imaging results of the first 39,438 participants are available. At this time point the following measurements were also repeated: hand grip strength and usual walking pace (17). Healthcare outcomes are available from self-reported data at recruitment and follow up visits, as well as linked electronic health records (primary care, hospital inpatient and death register).

UK Biobank application number: 102574

***Inclusion criteria***

* Baseline serum creatinine measurement
* Baseline serum cystatin-C measurement

***Baseline characteristics sample table***

|  |  |
| --- | --- |
| Characteristic | Total participants (n=XXX) |
| Male (n=XXX, %) | Female (n=XXX, %) | P value |
| Age (years) |  |  |  |
| Ethnic background |  |  |  |
| White |  |  |  |
| Mixed |  |  |  |
| Asian or Asian British |  |  |  |
| Black or Black British |  |  |  |
| Chinese |  |  |  |
| Other ethnic group |  |  |  |
| Do not know |  |  |  |
| Not answered |  |  |  |
|  |  |  |  |
| Smoking status |  |  |  |
| Never |  |  |  |
| Previous |  |  |  |
| Current |  |  |  |
| Not answered |  |  |  |
|  |  |  |  |
| Height (m) |  |  |  |
| Weight (kg) |  |  |  |
| BMI (kg/m2) |  |  |  |
|  |  |  |  |
| Serum urea (mmol/L) |  |  |  |
|  |  |  |  |
| Serum creatinine, baseline (umol/L) |  |  |  |
| Serum cystatin-C, baseline (mg/ml) |  |  |  |
| Sarcopenia Index, baseline |  |  |  |
|  |  |  |  |
| Handedness |  |  |  |
| Right |  |  |  |
| Left |  |  |  |
|  |  |  |  |
| Chronic disease (%) |  |  |  |
| Hypertension |  |  |  |
| Ischaemic heart disease |  |  |  |
| Stroke |  |  |  |
| Cancer |  |  |  |
| Chronic obstructive pulmonary disorder |  |  |  |
| Chronic kidney disease (stage 3-5) |  |  |  |
| Diabetes |  |  |  |

***Outcomes of interest sample table***

|  |  |
| --- | --- |
| Characteristic | Total participants (n=XXX) |
| Male (n=XXX, %) | Female (n=XXX, %) | P value |
| Total thigh FFMV, 2014 (L) |  |  |  |
| Anterior thigh FFMV, left, 2014 (L) |  |  |  |
| Anterior thigh FFMV, right, 2014 (L) |  |  |  |
| Posterior thigh FFMV, left, 2014 (L) |  |  |  |
| Posterior thigh FFMV, right, 2014 (L) |  |  |  |
|  |  |  |  |
| ALM, baseline (kg) |  |  |  |
| ALM, 2014 (kg) |  |  |  |
|  |  |  |  |
| Hand-grip strength |  |  |  |
| Dominant hand, baseline (kg) |  |  |  |
| Dominant hand, 2014 (kg) |  |  |  |
| Non-dominant hand, baseline (kg) |  |  |  |
| Non-dominant hand, 2014 (kg) |  |  |  |
|  |  |  |  |
| Self-reported walking pace |  |  |  |
| Slow, baseline |  |  |  |
| Slow, 2014 |  |  |  |
| Average, baseline |  |  |  |
| Average, 2014 |  |  |  |
| Brisk, baseline |  |  |  |
| Brisk, 2014 |  |  |  |

Categorical variables are presented as total number (%). Normally distributed continuous variables are presented as a mean (SD). Non-normally distributed continuous variables are presented as a median (IQR).

***Definitions of key terms***

*Sarcopenia Index*

Sarcopenia Index (creatinine/cystatin-Cx100) has been proposed as a biomarker of muscle quantity (2). Previous validation and correlation with muscle quantity has been with CT (surface area of the paraspinal muscles at L4). This has been previously validated in patients admitted to intensive care units and patients with lung cancer (3, 4).

*Fat free muscle volume (FFMV)*

Total thigh FFMV consists of the anterior thigh muscles (quadriceps femoris, sartorius and tensor fascia lata) and the posterior thigh muscles (gluteus, iliacus, adductor and hamstring muscles) from both legs. Fat free volume is defined as ‘the volume of all voxels with a fat fraction <50%’, this allows the muscle and fat volumes to be separated, giving a volume for viable muscle. Fat free muscle volume of the anterior and posterior thigh compartments was calculated from abdominal MRI scans using the AMRA (Advanced MR Analytics AB, AMRA, Sweden) Profiler system. Full methods of the MRI protocol and body composition profiling used in UK Biobank have been published (18, 19).

*Muscle fat infiltration (MFI)*

Muscle fat infiltration is defined as the fat fraction in the viable muscle tissue (fat-free muscle volume (FFMV)). The degree of intramuscular fat in the muscle is a quantifiable marker of muscle quality and has been studied across a number of different patient groups (20). The MFI percentage of the anterior and posterior thigh compartments was calculated from abdominal MRI scans using the AMRA (Advanced MR Analytics AB, AMRA, Sweden) Profiler system. Full methods of the MRI protocol and body composition profiling used in UK Biobank have been published (18, 19).

*Appendicular lean mass (ALM)*

Bioelectrical impedance measurements were taken at baseline for 492,184 participants. Measurement was performed using the Tanita BC418MA body composition analyser. A full protocol is available from UK Biobank. Appendicular fat-free mass will be calculated by adding the values for the left and right arm fat-free mass to the values for the left and right leg fat-free mass. This will then be converted to ALM as per the conversion equation developed by Dodds et al. (1), based on DEXA measurements in UK Biobank, removing the contribution of bone to appendicular fat-free mass.

ALM (kg) = (0.958 \* [Appendicular fat-free mass (kg)]) – (0.166 \* G) – 0.308

G taking value 0 if female and 1 if male.

*Hand-grip strength*

Hand-grip strength was measured at the 2014 imaging visit using a Jamar J00105 hydraulic hand dynamometer. The measurement protocol is freely available from UK Biobank. The units of measurement are in kg. Hand grip strength will be stratified into dominant and non-dominant hand measurements.

We will perform a secondary analysis using normalised values of hand grip strength by height2 and ideal body weight using the Devine formula (21).

*Self-reported walking pace*

Data was collected at the baseline visit using a touchscreen questionnaire. Participants were able to access the following information to answer the question*:* “Slow pace is defined as less than 3 miles per hour. Steady average pace is defined as between 3-4 miles per hour. Fast pace is defined as more than 4 miles per hour.”

**Statistical considerations**

***Software***

Data from the UK Biobank database will be viewed, processed and analysed in R (R Studio; 2022).

***Missing data***

Missing data will be handled using multiple imputation.

***Method of analysis***

Categorical variables will be presented as total numbers (%). Normally distributed continuous variables will be presented as a mean (SD). Non-normally distributed continuous variables will be presented as a median (IQR).

Means will be compared using the Students t-test, medians will be compared using the Wilcoxon-Mann-Whitney test. Categorical variables will be compared using the χ2 test.

The primary outcome measure will be assessed using a univariate linear regression model with SI as the independent variable. We will perform a multivariate analysis and consider age, sex and ethnicity within the model. If relationships are non-linear we will explore these by data transformation and/or polynomial regression. The association of SI with self-reported walking pace will be compared by groups (slow, steady average, fast pace) using analysis of variance (ANOVA).

***Sensitivity analysis***

A sensitivity analysis to ensure that our hypothesis holds true within the following subgroups will be performed.

* Age: <65, ≥65, ≥80
* Sex: Male, female
* BMI: Underweight <18.5, healthy 18.5 - 24.9, overweight 25 – 29.9, obesity 30 – 39.9, severe obesity >40
* Ethnicity: Mixed, Asian or Asian British, Black or Black British, Chinese, Other ethnic groups

**Workstream 2: Sarcopenia Index as a prognostic marker of health and multimorbidity**

**Background**

Multimorbidity, the presence of 2 or more long-term health conditions, is recognised as a growing healthcare challenge (22). It is associated with increased mortality (23), healthcare utilisation and costs (24). Patients with multimorbidity have been found to be at increased risk of sarcopenia (1); loss of muscle quantity and function. Sarcopenia is also closely linked with increased morbidity and mortality (7). The European Working Group on Sarcopenia in Older People (EWGSOP) suggest that the diagnosis of sarcopenia can be identified by low muscle strength and confirmed by low muscle quantity or quality (10). This can be challenging to diagnose in patients and requires multi-modal assessment with advanced imaging and dynamic studies of muscle strength.

Creatinine and cystatin-C are both biomarkers of kidney function. Creatinine is produced from muscle and therefore relies on muscle quantity, whereas cystatin-C is unaffected by muscle quantity. The sarcopenia index (SI, creatinine:cystatin-C x100) has been proposed as a biochemical estimate of muscle quantity and has been investigated in different patient groups (4, 5, 25). It has been shown to be associated with increased mortality and poor outcomes in patients admitted to intensive care (2, 3). Serum creatinine and cystatin-C are easily measured using a blood sample. This has obvious advantages for patients when compared to using a composite of hand grip strength, walking speed and imaging to diagnose sarcopenia.

We will investigate the prognostic ability of sarcopenia index to predict mortality and the development of multimorbidity. We will look at whether there is an association between sarcopenia index and future admission to hospital or intensive care. With respect to multimorbidity, we will look at the development of major adverse kidney events (MAKE), major adverse cardiac events (MACE), the correlation with the hospital frailty risk score and the acquisition of multimorbidity as a risk factor for in-hospital mortality, defined by the Charlson (26) and Elixhauser (27) comorbidity indices.

We hypothesise that patients with a low sarcopenia index may be at increased risk of mortality and the future development of multimorbidity. Investigating this interplay between multimorbidity, frailty and sarcopenia will allow us to better risk stratify patients, using sarcopenia index, who are at increased risk of developing adverse outcomes. Early identification and better risk stratification gives us a greater opportunity to instigate primary prevention for common chronic health conditions and begins to address the growing issue of multimorbidity.

**Study Objectives**

***Primary research questions***

Is baseline sarcopenia index a prognostic marker for mortality in adults?

***Secondary research questions***

Is baseline sarcopenia index a prognostic marker for future hospital admission, emergency surgery or critical care admission in adults?

Is baseline sarcopenia index a prognostic marker for the development of MAKE?

Is baseline sarcopenia index a prognostic marker for the development of MACE?

Does baseline sarcopenia index correlate with the Hospital Frailty Risk Score?

Does baseline sarcopenia index predict the development of multimorbidity, defined by the Charlson and Elixhauser comorbidity indices?

***Primary outcome***

Mortality (all-cause)

***Secondary outcomes***

Hospital encounter after baseline visit

* Inpatient hospital admission for >24 hours
	+ Medical
	+ Surgical (elective)
	+ Surgical (emergency)
* Critical care admission
	+ Medical
	+ Surgical (elective)
	+ Surgical (emergency)

The development of major adverse kidney events (MAKE) after baseline visit

The development of major adverse cardiac events (MACE) after baseline visit

The correlation of SI with Hospital Frailty Risk Score

The development of multimorbidity, defined by the Charleson and Elixhauser comorbidity indices

**Study population**

We will perform a longitudinal cohort study to investigate our objectives.

***Data source***

The data analysis will be carried out using a cohort of patients from the UK Biobank database. 500,000 participants aged 40-69 years old were recruited during 2006-2010 from the United Kingdom. A full assessment was performed at the recruitment visit including health questionnaires, measurements, and blood sample collection (16). Healthcare outcomes are available from self-reported data at recruitment and follow-up visits, as well as linked electronic health records (primary care, hospital inpatient and death register). The follow up period will be 8 years from recruitment.

UK Biobank application number: 102574

***Inclusion criteria***

* Baseline serum creatinine AND serum cystatin-C

***Baseline characteristics sample table***

|  |  |
| --- | --- |
| Characteristic | Total participants (n=XXX) |
| Male (n=XXX, %) | Female (n=XXX, %) | P value |
| Age (years) |  |  |  |
| Ethnic background |  |  |  |
| White |  |  |  |
| Mixed |  |  |  |
| Asian or Asian British |  |  |  |
| Black or Black British |  |  |  |
| Chinese |  |  |  |
| Other ethnic group |  |  |  |
| Do not know |  |  |  |
| Not answered |  |  |  |
|  |  |  |  |
| Height (m) |  |  |  |
| Weight (kg) |  |  |  |
| BMI (kg/m2) |  |  |  |
|  |  |  |  |
| Serum creatinine, baseline (umol/L) |  |  |  |
| Serum cystatin-C, baseline (mg/ml) |  |  |  |
| Sarcopenia Index, baseline |  |  |  |
|  |  |  |  |
| Chronic disease at baseline (%) |  |  |  |
| Hypertension |  |  |  |
| Ischaemic heart disease |  |  |  |
| Stroke |  |  |  |
| Cancer |  |  |  |
| Chronic obstructive pulmonary disorder |  |  |  |
| Chronic kidney disease (stage 3- 5) |  |  |  |
| Diabetes (type 1 and 2) |  |  |  |

***Outcomes of interest sample table***

|  |  |
| --- | --- |
| Characteristic | Total participants (n=XXX) |
| Male (n=XXX, %) | Female (n=XXX, %) | P value |
| Elixhauser comorbidity index |  |  |  |
| Charleson comorbidity index |  |  |  |
|  |  |  |  |
| Hospital inpatient encounter |  |  |  |
| Medical |  |  |  |
| Surgical (emergency) |  |  |  |
| Surgical (elective) |  |  |  |
| Critical care encounter |  |  |  |
| Medical |  |  |  |
| Surgical (emergency) |  |  |  |
| Surgical (elective) |  |  |  |
|  |  |  |  |
| All-cause mortality |  |  |  |
| MAKE |  |  |  |
| MACE |  |  |  |
|  |  |  |  |
| Hospital Frailty Risk Score |  |  |  |

Categorical variables are presented as total number (%). Normally distributed continuous variables are presented as a mean (SD). Non-normally distributed continuous variables are presented as a median (IQR).

***Definition of key terms***

*Sarcopenia Index*

Sarcopenia Index (SI, creatinine/cystatin-Cx100) has been proposed as a biomarker of muscle quantity (2). Previous validation and correlation with muscle quantity has been with CT (surface area of the paraspinal muscles at L4). This has been previously validated in patients admitted to intensive care units and patients with lung cancer (3, 4).

We will also consider normalisation of SI by height2.

*Major adverse kidney events (MAKE)*

Major adverse kidney events will be defined as the composite of the need for kidney replacement therapy (KRT) or a new diagnosis of CKD G3-5. If the data is available, we will define MAKE as the need for KRT, doubling of serum creatinine, fall of eGFR to <15ml.min/1.73m2 or a 30% decline in eGFR from baseline.

CKD will be classified as per the KDIGO staging system (28).

|  |  |  |  |
| --- | --- | --- | --- |
| **GFR Category** | **GFR (ml/min/1.73 m2 )** | **ACR Category** | **ACR mg/mmol** |
| G1 | ≥ 90 | A1 | <3 |
| G2 | 60 – 89 | A2 | 3 – 30  |
| G3A | 45 – 59 | A3 | > 30 |
| G3B | 30 – 44 |  |  |
| G4 | 15 – 29 |  |  |
| G5 | < 15 |  |  |

The development of CKD G3-5 will be identified using ICD-10 codes and associated primary care coding for creatinine values. We will use the CKD-EPI 2009 equation to calculate eGFRcys and eGFRcr (29). See Appendix, Table 1 for associated clinical coding.

*Major adverse cardiac events (MACE)*

Major adverse cardiac events will be defined as the composite of myocardial infarction, heart failure, revascularisation (including percutaneous coronary intervention and coronary artery bypass grafting) or stroke. These will be identified from primary and secondary care clinical coding. See Appendix, Table 1 for associated clinical coding.

*Hospital Frailty Risk Score*

The Hospital Frailty Risk Score is a tool that has been developed to identify frailty from ICD-10 codes (30). It has been shown to identify those who are at risk of adverse outcomes associated with frailty. See Appendix, Table 3 for associated clinical coding.

*Charlson and Elixhauser comorbidity indices*

The Charlson (26) and Elixhauser (27) comorbidity indices are methods of weighting and adjusting comorbid conditions and the effects that they may have on the risk of in-hospital mortality.

**Statistical considerations**

***Software***

Data from the UK Biobank database will be viewed, processed and analysed in R (R Studio; 2022).

***Missing data***

Missing data will be handled using multiple imputation.

***Method of analysis***

Categorical variables will be presented as total number (%). Normally distributed continuous variables will be presented as a mean (SD). Non-normally distributed continuous variables will be presented as a median (IQR).

Means will be compared using the Students t-test, medians will be compared using the Wilcoxon-Mann-Whitney test. Categorical variables will be compared using the χ2 test.

The risk associated with SI and all-cause mortality, hospital admission and the development of MAKE and MACE will be explored using Cox-proportional hazards. Time-to-event analysis will be performed by calculating Kaplan-Meir curves and the log-rank test to evaluate the association between SI and all-cause mortality, hospital admission and the development of MAKE and MACE.

We will investigate the relationship between SI and the Hospital Frailty Risk Score, Charlson and Elixhauser comorbidity indices using linear regression models. Interaction terms that we will consider are age, sex and ethnicity. If relationships are non-linear we will explore these by data transformation and/or polynomial regression.

***Sensitivity analysis***

A sensitivity analysis to ensure that our hypothesis holds true within the following subgroups will be performed.

* Age: <65, ≥65, ≥80
* Sex: Male, female
* BMI: Underweight <18.5, healthy 18.5 - 24.9, overweight 25 – 29.9, obesity 30 – 39.9, severe obesity >40
* Ethnicity: Mixed, Asian or Asian British, Black or Black British, Chinese, Other ethnic groups

**Workstream 3: Comparison of cystatin-C vs creatinine as a prognostic measure of kidney function**

**Background**

The links between chronic kidney disease (CKD), increased mortality and cardiovascular disease have been well established (31). CKD is implicated in multimorbidity and poses a significant healthcare burden, particularly in the future (32, 33, 34). The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend estimating glomerular filtration rate (GFR) using the CKD-EPI formula and creatinine for both CKD and acute kidney injury (AKI) (28, 35). Creatinine is an imperfect biomarker for GFR, it is influenced by age, sex, ethnicity, muscle quantity, diet, and certain drugs (36). Cardiovascular disease and its associated complications and risk factors are well studied, with established primary prevention strategies (37). The identification and prevention of kidney disease is steadily gaining momentum and we have seen significant advances in primary prevention over the last few years(38). Our ageing and multimorbid population is at an increased risk of sarcopenia; loss of muscle quantity (1). With creatinine being so reliant on muscle quantity, are we missing a proportion of patients with modifiable kidney disease?

Cystatin-C is a glomerular filtration biomarker which is easily measured in serum. Whilst there are factors that can affect cystatin-C such as smoking status, it is not linked with muscle quantity (39). It is recommended for use by KDIGO in circumstances where creatinine may not be accurate for classifying CKD. Despite this, its uptake is not well established in current UK practice. Sarcopenia index (SI, creatinine:cystatin-C x100) has been proposed as a biochemical estimate of muscle quantity and has been investigated in different patient groups (2, 5, 25). It has been shown to be associated with increased mortality in intensive care and lung cancer patients (3, 4).

Cystatin-C has been found to correlate with the early development of AKI in various inpatient populations such as post-cardiac surgery (40, 41) and critical care (42). It has shown better performance than creatinine as a prognostic marker for the future development of CKD, mortality and associated cardiovascular complications in patients with an eGFR >45ml/min/1.73 m2 (43), this finding has also been demonstrated in elderly patients aged over 65 with an eGFR >60ml/min/1.73m2(44) as well as general population cohorts (45). eGFRcys has also been investigated as a predictor for mortality in the intensive care population, with superior results when compared to eGFRcr (46).

A Swedish prospective cohort study of 274 intensive care patients identified the increased prevalence of CKD, using eGFRcys, at 3 months following AKI (47). They excluded patients with CKD stage 3 or above, which is a known risk factor for the development of AKI (48, 49). Furthermore, an episode of AKI is closely linked with hospital and critical care admission(50), as well as subsequent worsening of CKD and development of end stage kidney disease (ESKD) (48, 51, 52).

We will examine the relationship of eGFR calculated using cystatin-C in the CKD-EPI formula (eGFRcys) with baseline sarcopenia index and eGFRcr:eGFRcys. We will also compare this to using creatinine alone(eGFRcr) and combined with cystatin-C (eGFRcr-cys). We hypothesise that those at extremes of muscle quantity will have a greater discrepancy between eGFRcys and eGFRcr.

We will also investigate whether using glomerular filtration rate estimated by eGFRcys as a measure of kidney disease, is more closely related to an increased risk of hospital admission, critical care admission and episodes of acute kidney injury (AKI), than eGFRcr and eGFRcr-cys across all CKD stages.

The implications of these findings would strengthen the argument behind using eGFRcsy during states of fluctuating muscle mass, such as during acute illness and the subsequent recovery periods. It would enable us to better predict which patients are at increased risk of AKI and future hospital and critical care admission, enabling us to instigate earlier primary prevention and risk modification.

**Study Objectives**

***Primary research questions***

Which measures of kidney function and sarcopenia at baseline best predict CKD status at the time of last follow up?

* eGFRcr
* eGFRcys
* eGFRcr-cys
* SI
* eGFRcr:eGFRcys

***Secondary research questions***

Does classifying kidney disease using eGFRcys improve the prediction of the development of AKI compared with eGFRcr and eGFRcr-cys?

Does classifying kidney disease using eGFRcys improve the prediction of future hospital or critical care admission compared with eGFRcr and eGFRcr-cys?

***Primary outcomes***

CKD status (G1-5) at time of last follow-up (creatinine)

***Secondary outcomes***

Episode of AKI after baseline visit

Hospital encounter after baseline visit

* Inpatient hospital admission for >24 hours
	+ Medical
	+ Surgical (elective)
	+ Surgical (emergency)
* Critical care admission
	+ Medical
	+ Surgical (elective)
	+ Surgical (emergency)

**Study population**

We will perform a cross-sectional cohort study to investigate our objectives.

***Data source***

The data analysis will be carried out using a cohort of patients from the UK Biobank database. 500,000 participants aged 40-69 years old were recruited during 2006-2010 from the United Kingdom. A full assessment was performed at the recruitment visit including health questionnaires, measurements, and blood sample collection (16). Healthcare outcomes are available from self-reported data at recruitment and follow up visits, as well as linked electronic health records (primary care, hospital inpatient and death register).

UK Biobank application number: 102574

***Inclusion criteria***

* Baseline serum creatinine AND baseline serum cystatin-C

***Baseline characteristics sample table (will also be replicated for eGFRcys and eGFRcr-cys***

|  |  |
| --- | --- |
| Characteristic | Total participants (n=XXX) |
| eGFRcr (ml/min/1.73m2) |
|  | >90 | 60-89 | 45-59 | 30-44 | 15-29 | <15 |
| Age (years) |  |  |  |  |  |  |
| Sex |  |  |  |  |  |  |
| Male |  |  |  |  |  |  |
| Female |  |  |  |  |  |  |
| Ethnic background |  |  |  |  |  |  |
| White |  |  |  |  |  |  |
| Mixed |  |  |  |  |  |  |
| Asian or Asian British |  |  |  |  |  |  |
| Black or Black British |  |  |  |  |  |  |
| Chinese |  |  |  |  |  |  |
| Other ethnic group |  |  |  |  |  |  |
| Do not know |  |  |  |  |  |  |
| Not answered |  |  |  |  |  |  |
| Height (m) |  |  |  |  |  |  |
| Weight (kg) |  |  |  |  |  |  |
| BMI (kg/m2) |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Serum urea, baseline (mmol/L) |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Serum creatinine, baseline (umol/L) |  |  |  |  |  |  |
| Serum cystatin-C, baseline (mg/ml) |  |  |  |  |  |  |
| Sarcopenia Index, baseline |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Urine ACR, baseline (mg/mmol) |  |  |  |  |  |  |
| <3 |  |  |  |  |  |  |
| 3 - 30 |  |  |  |  |  |  |
| >30 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Chronic disease at baseline (%) |  |  |  |  |  |  |
| Hypertension |  |  |  |  |  |  |
| Ischaemic heart disease |  |  |  |  |  |  |
| Stroke |  |  |  |  |  |  |
| Cancer |  |  |  |  |  |  |
| Chronic obstructive pulmonary disorder |  |  |  |  |  |  |
| Diabetes (type 1 and 2) |  |  |  |  |  |  |

***Outcomes of interest sample table***

|  |  |
| --- | --- |
| Characteristic | Total participants (n=XXX) |
| **eGFRcr** | >90 | 60-89 | 45-59 | 30-44 | 15-29 | <15 |
| Acute Kidney Injury |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Hospital inpatient encounter |  |  |  |  |  |  |
| Medical |  |  |  |  |  |  |
| Surgical (emergency) |  |  |  |  |  |  |
| Surgical (elective) |  |  |  |  |  |  |
| Critical care encounter |  |  |  |  |  |  |
| Medical |  |  |  |  |  |  |
| Surgical (emergency) |  |  |  |  |  |  |
| Surgical (elective) |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **eGFRcys** | >90 | 60-89 | 45-59 | 30-44 | 15-29 | <15 |
| Acute Kidney Injury |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Hospital inpatient encounter |  |  |  |  |  |  |
| Medical |  |  |  |  |  |  |
| Surgical (emergency) |  |  |  |  |  |  |
| Surgical (elective) |  |  |  |  |  |  |
| Critical care encounter |  |  |  |  |  |  |
| Medical |  |  |  |  |  |  |
| Surgical (emergency) |  |  |  |  |  |  |
| Surgical (elective) |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **eGFRcr-cys** | >90 | 60-89 | 45-59 | 30-44 | 15-29 | <15 |
| Acute Kidney Injury |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| Hospital inpatient encounter |  |  |  |  |  |  |
| Medical |  |  |  |  |  |  |
| Surgical (emergency) |  |  |  |  |  |  |
| Surgical (elective) |  |  |  |  |  |  |
| Critical care encounter |  |  |  |  |  |  |
| Medical |  |  |  |  |  |  |
| Surgical (emergency) |  |  |  |  |  |  |
| Surgical (elective) |  |  |  |  |  |  |

Categorical variables are presented as total number (%). Normally distributed continuous variables are presented as a mean (SD). Non-normally distributed continuous variables are presented as a median (IQR).

***Definition of key terms***

*Chronic Kidney Disease*

Chronic Kidney Disease will be classified as per the KDIGO staging system (28).

|  |  |  |  |
| --- | --- | --- | --- |
| **GFR Category** | **GFR (ml/min/1.73 m2 )** | **ACR Category** | **ACR mg/mmol** |
| G1 | ≥ 90 | A1 | <3 |
| G2 | 60 – 89 | A2 | 3 – 30  |
| G3A | 45 – 59 | A3 | > 30 |
| G3B | 30 – 44 |  |  |
| G4 | 15 – 29 |  |  |
| G5 | < 15 |  |  |

CKD will be identified using ICD-10 codes and associated primary care coding for creatinine values. We will use the CKD-EPI 2021 equations without race to calculate eGFRcys and eGFRcr (29).

*Acute Kidney Injury*

Acute kidney injury will be identified from HES, death records and primary care data. See Appendix, Table 2 for associated clinical coding.

*Sarcopenia Index*

Sarcopenia Index (creatinine/cystatin-Cx100) has been proposed as a biomarker of muscle quantity (2). Previous validation and correlation with muscle quantity has been with CT (surface area of the paraspinal muscles at L4). This has been previously validated in patients admitted to intensive care units and patients with lung cancer (3, 4).

We will also consider normalisation of SI by height2.

**Statistical considerations**

***Software***

Data from the UK Biobank database will be viewed, processed and analysed in R (R Studio; 2022).

***Missing data***

Missing data will be handled using multiple imputation.

***Method of analysis***

Categorical variables will be presented as total number (%). Normally distributed continuous variables will be presented as a mean (SD). Non-normally distributed continuous variables will be presented as a median (IQR).

Means will be compared using the Students t-test, medians will be compared using the Wilcoxon-Mann-Whitney test. Categorical variables will be compared using the χ2 test.

We will investigate the relationship between the development of CKD G3+ and the predictors of baseline eGFRcr, eGFRcys, eGFRcr-cys, SI or GFR ratio (eGFRcr:eGFRcys) using multivariate logistic regression. We will include baseline eGFR, age, sex, SI or GFR ratio(eGFRcr:eGFRcys) as variables and allow for a potential liner interaction between baseline eGFR and age. We will fit continuous variables as restricted cubic splines.

We will calculate the risk of developing AKI for each eGFRcys category using cox proportional hazards. We will do the same analysis for eGFRcr and eGFRcr-cys categories and compare the two. We will calculate the risk of a hospital encounter (inpatient and critical care, categories as detailed) for each eGFRcys category using the same methods as above. We will do the same analysis for eGFRcr and eGFRcr-cys categories and compare the two.

Interaction terms that we will consider are age, sex and ethnicity.

***Sensitivity analysis***

A sensitivity analysis to ensure that our hypothesis holds true within the following subgroups will be performed.

* Age: <65, ≥65, ≥80
* Sex: Male, female
* BMI: Underweight <18.5, healthy 18.5 - 24.9, overweight 25 – 29.9, obesity 30 – 39.9, severe obesity >40
* Ethnicity: Mixed, Asian or Asian British, Black or Black British, Chinese, Other ethnic groups

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**Appendix – Table 1. Associated clinical coding for MAKE and MACE**

|  |
| --- |
| **Kidney Replacement Therapy** |
| **Source** | **Associated code** |
| UK Biobank algorithmic defined outcomes1: ESRD | End stage renal disease treated with renal replacement therapy (HD, PD, transplant) |
| Self-reported illness data | Renal failure requiring dialysis |
| ICD-10 | I77.0 Arteriovenous fistula, acquiredN16.5 Renal tubulo-interstitial disorders in transplant rejectionQ60.1 Renal agenesis, bilateralT82.4 Mechanical complication of vascular dialysis catheterT86.1 Kidney transplant failure and rejectionY60.2 Unintentional cut, puncture, perforation or haemorrhage during surgical and medical care - During kidney dialysis or other perfusionY61.2 Foreign object accidentally left in body during surgical and medical care - During kidney dialysis or other perfusionY62.2 Failure of sterile precautions during surgical and medical care - During kidney dialysis or other perfusionY84.1 Other medical procedures as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure - Kidney dialysisZ49.X2 Care involving dialysisZ94.0 Kidney transplant statusZ99.2 Dependence on renal dialysis |
| ICD 9 | E870.2 Accidental cut, puncture, perforation or hemorrhage during kidney dialysis or other perfusionE871.2 Foreign object left in body during kidney dialysis or other perfusionE872.2 Failure of sterile precautions during kidney dialysis and other perfusionE874.2 Mechanical failure of instrument or apparatus during kidney dialysis and other perfusionE879.1 Kidney dialysis as the cause of abnormal reaction of patient, or of later complication, without mention of misadventure at time of procedureV42.0 Organ or tissue replaced by transplant - KidneyV45.1 Renal dialysis statusV56.X2 Aftercare involving intermittent dialysis447.0 Arteriovenous fistula, acquired753.0 Renal agenesis and dysgenesis |
| OPCS-4 | L74.2 Creation of arteriovenous fistula NECL74.4 Banding of arteriovenous fistulaL74.5 Thrombectomy of arteriovenous fistulaL74.6 Creation of graft fistula for dialysisL74.7 Injection of radiocontrast substance into arteriovenous fistulaL75.2 Repair of acquired arteriovenous fistulaM01.X2 Transplantation of kidneyM02.3 Bilateral nephrectomyM02.6 Excision of rejected transplanted kidneyM02.7 Excision of transplanted kidney NECM08.4 Exploration of transplanted kidneyM17 Interventions associated with transplantation of kidneyM17.2 Pre-transplantation of kidney work-up – recipientM17.4 Post-transplantation of kidney examination – recipientM17.8 Other specified interventions associated with transplantation of kidneyM17.9 Unspecified interventions associated with transplantation of kidneyX40 Compensation for renal failureX40.1 Renal dialysisX40.2 Peritoneal dialysis NECX40.3 Haemodialysis NECX40.4 HaemofiltrationX40.5 Automated peritoneal dialysisX40.6 Continuous ambulatory peritoneal dialysisX40.8 Other specified compensation for renal failureX40.9 Unspecified compensation for renal failureX41.X2 Placement of ambulatory apparatus for compensation for renal failureX42.X2 Placement of other apparatus for compensation for renal failure |
| READ V2 | Read code list generated using the UK Biobank mapping for primary care data from ICD-10 and ICD-9 codes as well as the following search terms: end stage, end-stage, dialysis, transplant, arteriovenous |
| READ CTV3 |
| **New diagnosis of CKD 3-5** |
| ICD-10 | N18.3 Chronic kidney disease, stage 3N18.4 Chronic kidney disease, stage 4N18.5 Chronic kidney disease, stage 5 |
| READ V2 | Terms matching a description of: Chronic Kidney Disease Stage 3- 5Read code list generated using the UK Biobank mapping for primary care data from ICD-10 and ICD-9 codes as well as the following search terms: chronic renal, chronic kidney |
| READ CTV3 |
| **Creatinine values** |
| Read V2 | 44J3, 44JC, 44JD, 44JF, 4Q40Exclude if associated AKI codes (Table 2) or emergency hospital admission (below) **within 5 days** of creatinine result. |
| Read CTV3 |
| **Emergency hospital admission** |
| Read V2 | 8H2., 8H21, 8H22, 8H23, 8H230, 8H24, 8H26, 8H27, 8H28, 8H29, 8H2A, 8H2B, 8H2C, 8H2D, 8H2E, 8H2F, 8H2G, 8H2H, 8H2I, 8H2J, 8H2K, 8H2L, 8H2M, 8H2N, 8H2O, 8H2P, 8H2Q, 8H2R, 8H2S, 8H2V, 8H2W, 8H2X, 8H2Y, 8H2Z, 8Hb, 8Hd1, 8Hd3, 8Hd5, 8Hd6 |
| Read CTV3 |
| **Myocardial infarction and unstable angina** |
| UK Biobank algorithmic defined outcomes1: Myocardial infarction | Myocardial infarction, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) |
| Self-reported illness data | Heart attack/myocardial infarction |
| ICD-10 | 120.0 Unstable anginaI21.X2 Acute myocardial infarctionI22.X2 Subsequent myocardial infarction I23.X2 Certain current complications following acute myocardial infarction I24.1 Dressler's syndrome124.8 Other forms of acute ischemic heart disease124.9 Acute ischemic heart disease, unspecifiedI25.2 Old myocardial infarction |
| ICD 9 | 410 Acute myocardial infarction 411 Other acute and subacute forms of ischaemic heart disease412 Old myocardial infarction |
| READ V2 | Read code list generated using the UK Biobank mapping for primary care data from ICD-10 and ICD-9 codes as well as the following search terms: unstable, angina, myocardial infarction, myocardial ischaemia, acute coronary syndrome, heart attack, ischaemic heart. |
| READ CTV3 |
| **Heart Failure** |
| Self-reported illness data | Heart failure/pulmonary oedema |
| ICD 10 | I11.0 Hypertensive heart disease with (congestive) heart failureI13.0 Hypertensive heart and renal disease with (congestive) heart failureI13.2 Hypertensive heart and renal disease with both (congestive) heart failure and renal failureI50.X2 Heart failure |
| ICD 9 | 428.X2 Heart failure |
| OPCS-4 | K54.1 Open implantation of ventricular assist deviceK54.2 Open removal of ventricular assist deviceK56.2 Transluminal insertion of heart assist system NECK56.3 Transluminal maintenance of heart assist systemK56.4 Transluminal removal of heart assist systemK56.8 Other specified transluminal heart assist operationsK56.9 Unspecified transluminal heart assist operationsU54.1 Rehabilitation for heart failureY70.5 Implantation of ventricular assist device |
| READ V2 | Read code list generated using the UK Biobank mapping for primary care data from ICD-10 and ICD-9 codes as well as the following search terms: heart failure, cardiac failure, cardiac insufficiency, ventricular failure, new york heart, acute pulmonary oedema, biventricular, ventricular assist. |
| READ CTV3 |
| **Revascularisation (PCI and CABG)** |
| ICD 10 | Z95.5 Presence of coronary angioplasty implant and graft |
| ICD 9 | V434 Blood vessel replaced by other means |
| OPCS-4 | K40.X2 Saphenous vein graft replacement of coronary arteryK41.X2 Other autograft replacement of coronary arteryK42.X2 Allograft replacement of coronary arteryK43.X2 Prosthetic replacement of coronary arteryK44.X2 Other replacement of coronary arteryK45.X2 Connection of thoracic artery to coronary arteryK46.X2 Other bypass of coronary arteryK47.1 Endarterectomy of coronary arteryK48.3 Open angioplasty of coronary arteryK48.4 Exploration of coronary arteryK48.8 Other specified other open operation on coronary arteryK48.9 Other open operation on coronary artery nosK49.X2 Transluminal balloon angioplasty of coronary arteryK50.X2 Other therapeutic transluminal operations on coronary artery K75.X2 Percutaneous transluminal balloon angioplasty of one coronary artery |
| READ V2 | Read code list generated using the UK Biobank mapping for primary care data from ICD-10 and ICD-9 codes as well as the following search terms: coronary artery, percutaneous coronary. |
| READ CTV3 |
| **Stroke** |
| UK Biobank algorithmic defined outcomes1: Stroke | Any stroke, ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage |
| Self-reported illness data | StrokeSubarachnoid haemorrhage Brain haemorrhage Ischaemic stroke |
| ICD-10 | I60.X2 Subarachnoid haemorrhage I61.X2 Intracerebral haemorrhage I63 Cerebral infarction I63.X2 Cerebral infarction due to thrombosis of precerebral arteries I64 Stroke, not specified as haemorrhage or infarctionI69.X2 Sequelae of cerebrovascular disease |
| ICD 9 | 430 Subarachnoid haemorrhage 431 Intracerebral haemorrhage433.X2 Occlusion and stenosis of precerebral arteries 434.X2 Occlusion of cerebral arteries 436 Acute, but ill-defined, cerebrovascular disease438 Late effects of cerebrovascular disease |
| OPCS-4 | A05.2 Evacuation of haematoma from temporal lobe of brainA05.3 Evacuation of haematoma from cerebellumA05.4 Evacuation of intracerebral haematoma NECA10.3 Aspiration of haematoma of tissue of brainA22.1 Drainage of subarachnoid space of brainL33.2 Clipping of aneurysm of cerebral arteryO01.X2 Transluminal coil embolisation of aneurysm of arteryO02.X2 Transluminal balloon assisted coil embolisation of aneurysm of arteryO03.X2 Transluminal stent assisted coil embolisation of aneurysm of arteryO04.X2 Other transluminal embolisation of aneurysm of arteryU54.3 Delivery of rehabilitation for stroke |
| READ V2 | Read code list generated using the UK Biobank mapping for primary care data from ICD-10 and ICD-9 codes as well as the following search terms: stroke, ischaemic stroke, intracerebral haemorrhage, cerebral haemorrhage, subarachnoid haemorrhage, cerebrovascular disease, clipping, coil, evacuation, aspiration of haematoma |
| READ CTV3 |
| 1 Includes self-reported illness data, hospital inpatient data and death register data2 The ICD codes suffixed X stands for any code with the preceding figures |

**Appendix – Table 2. Associated clinical coding for AKI**

|  |  |
| --- | --- |
| **Source** | **Associated code** |
| ICD-10 | N17.X1 Acute renal failureO90.4 Postpartum acute renal failure |
| ICD 9 | 584 Acute renal failure584.5 - With lesion of tubular necrosis584.6 - With lesion of renal cortical necrosis584.7 - With lesion of renal medullary (papillary) necrosis 584.8 - With other specified pathological lesion in kidney 584.9 - Unspecified669.3 Acute renal failure following labour and delivery |
| OPCS-4 | X40.4 Haemofiltration |
| READ V2 | Read code list generated using the UK Biobank mapping for primary care data from ICD-10 and ICD-9 codes as well as the following search terms: acute kidney, acute renal, haemofiltration. |
| READ CTV3 |
| 1 TheICD codes suffixed X stands for any code with the preceding figures |

**Appendix – Table 3. Associated clinical coding for Hospital Frailty Risk Score**

Model developed by Gilbert et al. (30)

|  |  |  |
| --- | --- | --- |
| **ICD10 Code** | **Description** | **Points awarded** |
| F00 | Dementia in Alzheimer's disease | 7·1 |
| G81 | Hemiplegia | 4·4 |
| G30 | Alzheimer's disease | 4·0 |
| I69 | Sequelae of cerebrovascular disease (secondary codes) | 3·7 |
| R29 | Other symptoms and signs involving the nervous and musculoskeletal systems (R29·6 Tendency to fall) | 3·6 |
| N39 | Other disorders of urinary system (includes urinary tract infection and urinary incontinence) | 3·2 |
| F05 | Delirium, not induced by alcohol and other psychoactive substances | 3·2 |
| W19 | Unspecified fall | 3·2 |
| S00 | Superficial injury of head | 3·2 |
| R31 | Unspecified haematuria | 3·0 |
| B96 | Other bacterial agents as the cause of diseases classified to other chapters (secondary code) | 2·9 |
| R41 | Other symptoms and signs involving cognitive functions and awareness | 2·7 |
| R26 | Abnormalities of gait and mobility | 2·6 |
| I67 | Other cerebrovascular diseases | 2·6 |
| R56 | Convulsions, not elsewhere classified | 2·6 |
| R40 | Somnolence, stupor and coma | 2·5 |
| T83 | Complications of genitourinary prosthetic devices, implants and grafts | 2·4 |
| S06 | Intracranial injury | 2·4 |
| S42 | Fracture of shoulder and upper arm | 2·3 |
| E87 | Other disorders of fluid, electrolyte and acid base balance | 2·3 |
| M25 | Other joint disorders, not elsewhere classified | 2·3 |
| E86 | Volume depletion | 2·3 |
| R54 | Senility | 2·2 |
| Z50 | Care involving use of rehabilitation procedures | 2·1 |
| F03 | Unspecified dementia | 2·1 |
| W18 | Other fall on same level | 2·1 |
| Z75 | Problems related to medical facilities and other health care | 2·0 |
| F01 | Vascular dementia | 2·0 |
| S80 | Superficial injury of lower leg | 2·0 |
| L03 | Cellulitis | 2·0 |
| H54 | Blindness and low vision | 1·9 |
| E53 | Deficiency of other B group vitamins | 1·9 |
| Z60 | Problems related to social environment | 1·8 |
| G20 | Parkinson's disease | 1·8 |
| R55 | Syncope and collapse | 1·8 |
| S22 | Fracture of rib(s), sternum and thoracic spine | 1·8 |
| K59 | Other functional intestinal disorders | 1·8 |
| N17 | Acute renal failure | 1·8 |
| L89 | Decubitus ulcer | 1·7 |
| Z22 | Carrier of infectious disease | 1·7 |
| B95 | Streptococcus and staphylococcus as the cause of diseases classified to other chapters | 1·7 |
| L97 | Ulcer of lower limb, not elsewhere classified | 1·6 |
| R44 | Other symptoms and signs involving general sensations and perceptions | 1·6 |
| K26 | Duodenal ulcer | 1·6 |
| I95 | Hypotension | 1·6 |
| N19 | Unspecified renal failure | 1·6 |
| A41 | Other septicaemia | 1·6 |
| Z87 | Personal history of other diseases and conditions | 1·5 |
| J96 | Respiratory failure, not elsewhere classified | 1·5 |
| X59 | Exposure to unspecified factor | 1·5 |
| M19 | Other arthrosis | 1·5 |
| G40 | Epilepsy | 1·5 |
| M81 | Osteoporosis without pathological fracture | 1·4 |
| S72 | Fracture of femur | 1·4 |
| S32 | Fracture of lumbar spine and pelvis | 1·4 |
| E16 | Other disorders of pancreatic internal secretion | 1·4 |
| R94 | Abnormal results of function studies | 1·4 |
| N18 | Chronic renal failure | 1·4 |
| R33 | Retention of urine | 1·3 |
| R69 | Unknown and unspecified causes of morbidity | 1·3 |
| N28 | Other disorders of kidney and ureter, not elsewhere classified | 1·3 |
| R32 | Unspecified urinary incontinence | 1·2 |
| G31 | Other degenerative diseases of nervous system, not elsewhere classified | 1·2 |
| Y95 | Nosocomial condition | 1·2 |
| S09 | Other and unspecified injuries of head | 1·2 |
| R45 | Symptoms and signs involving emotional state | 1·2 |
| G45 | Transient cerebral ischaemic attacks and related syndromes | 1·2 |
| Z74 | Problems related to care-provider dependency | 1·1 |
| M79 | Other soft tissue disorders, not elsewhere classified | 1·1 |
| W06 | Fall involving bed | 1·1 |
| S01 | Open wound of head | 1·1 |
| A04 | Other bacterial intestinal infections | 1·1 |
| A09 | Diarrhoea and gastroenteritis of presumed infectious origin | 1·1 |
| J18 | Pneumonia, organism unspecified | 1·1 |
| J69 | Pneumonitis due to solids and liquids | 1·0 |
| R47 | Speech disturbances, not elsewhere classified | 1·0 |
| E55 | Vitamin D deficiency | 1·0 |
| Z93 | Artificial opening status | 1·0 |
| R02 | Gangrene, not elsewhere classified | 1·0 |
| R63 | Symptoms and signs concerning food and fluid intake | 0·9 |
| H91 | Other hearing loss | 0·9 |
| W10 | Fall on and from stairs and steps | 0·9 |
| W01 | Fall on same level from slipping, tripping and stumbling | 0·9 |
| E05 | Thyrotoxicosis [hyperthyroidism] | 0·9 |
| M41 | Scoliosis | 0·9 |
| R13 | Dysphagia | 0·8 |
| Z99 | Dependence on enabling machines and devices | 0·8 |
| U80 | Agent resistant to penicillin and related antibiotics | 0·8 |
| M80 | Osteoporosis with pathological fracture | 0·8 |
| K92 | Other diseases of digestive system | 0·8 |
| I63 | Cerebral Infarction | 0·8 |
| N20 | Calculus of kidney and ureter | 0·7 |
| F10 | Mental and behavioural disorders due to use of alcohol | 0·7 |
| Y84 | Other medical procedures as the cause of abnormal reaction of the patient | 0·7 |
| R00 | Abnormalities of heart beat | 0·7 |
| J22 | Unspecified acute lower respiratory infection | 0·7 |
| Z73 | Problems related to life-management difficulty | 0·6 |
| R79 | Other abnormal findings of blood chemistry | 0·6 |
| Z91 | Personal history of risk-factors, not elsewhere classified | 0·5 |
| S51 | Open wound of forearm | 0·5 |
| F32 | Depressive episode | 0·5 |
| M48 | Spinal stenosis (secondary code only) | 0·5 |
| E83 | Disorders of mineral metabolism | 0·4 |
| M15 | Polyarthrosis | 0·4 |
| D64 | Other anaemias | 0·4 |
| L08 | Other local infections of skin and subcutaneous tissue | 0·4 |
| R11 | Nausea and vomiting | 0·3 |
| K52 | Other noninfective gastroenteritis and colitis | 0·3 |
| R50 | Fever of unknown origin | 0·1 |