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Complete List of Authors:	Gagesch, Michael; University Hospital Zurich, Department of Geriatrics Edler, Karin; University Hospital Zurich, Clinical Trails Center Chocano-Bedoya, Patricia; University Hospital Zurich, Centre on Aging and Mobility; University of Bern, Institute of Primary Health Care (BIHAM) Abderhalden, Lauren; University Hospital Zurich, Centre on Aging and Mobility Seematter-Bagnoud , Laurence; Center for Primary Care and Public Health , Epidemiology and Health systems; University Hospital of Lausanne, Geriatric Medicine and Rehabilitation Meyer, Tobias; Universitäre Altersmedizin FELIX PLATTER Bertschi, Dominic; Spital Tiefenau Zekry, Dina; Geneva University Hospitals and University of Geneva, Department of Internal Medicine, Rehabilitation and Geriatrics, Division of Geriatrics Bula, Christophe; University of Lausanne Medical Center (CHUV), Service of Geriatric Medicine & Geriatric Rehabilitation Gold, Gabriel; University Hospitals Geneva, Department of Rehabilitation and Geriatrics Kressig, Reto; Universitäre Altersmedizin FELIX PLATTER Stuck, Andreas; Inselspital Universitatsspital Bern, University Department of Geriatrics Bischoff-Ferrari, Heike; University Hospital Zurich, Department of Geriatrics
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Swiss Frailty Network & Repository – Rationale and Design of a Swiss Personalized Health Network's Driver Project Observational Study

Michael Gagesch[1,2], Karin Edler[3], Patricia O. Chocano-Bedoya[2,4], Lauren A. Abderhalden[2], Laurence Seematter-Bagnoud[5], Tobias Meyer[6], Dominic Bertschi[6,7] Dina Zekry[8], Christophe J. Büla[5], Gabriel Gold[8], Reto W. Kressig[6], Andreas E. Stuck[7], and Heike A. Bischoff-Ferrari[1,2,9]

Affiliations

[1] Department of Geriatrics, University Hospital Zurich, Zurich, Switzerland
[2] Centre on Aging and Mobility, University Hospital Zurich and University of Zurich, Zurich, Switzerland
[3] Research Data Service Center, University Hospital Zurich, Zurich, Switzerland
[4] Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
[5] Service of Geriatric Medicine and Geriatric Rehabilitation, Lausanne University Hospital, Lausanne, Switzerland
[6] University Department of Geriatric Medicine FELIX PLATTER, Basel, Switzerland
[7] Department of Geriatrics, Inselspital, University Hospital Bern, and University of Bern, Bern, Switzerland
[8] Department of Rehabilitation and Geriatrics, University Hospitals Geneva, Geneva, Switzerland
[9] City Hospital Waid and Triemli, Zurich, Switzerland

Corresponding Author

Michael Gagesch, MD

Dept. of Geriatrics

University Hospital Zurich

Zurich, Switzerland

Email: michael.gagesch@usz.ch

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Abstract

Introduction: Early identification of frailty by clinical instruments or accumulation of deficit indexes can contribute to improve health care for older adults, including the prevention of negative outcomes in acute care. However, conflicting evidence exists on how to best capture frailty in this setting. Simultaneously, the increasing utilization of electronic health records (EHR) opens up new possibilities for research and patient care, including frailty.

Methods and analysis: The Swiss Frailty Network and Repository (SFNR) primarily aims to develop an electronic Frailty Index (eFI) from routinely available EHR data, validate it against a test-based clinical Frailty Instrument (cFI) and to investigate both tools' predictive ability against length of stay and in-hospital mortality, two important outcomes in acute care. As a Swiss Personalized Health Network (SPHN) driver project, we will connect all five Swiss University Hospitals' Geriatric Departments with a representative sample of patients aged 65 years and older admitted to acute care. Our study will report on the characteristics and usability of the first nationwide eFI in Switzerland, validated against a test-based cFI.

Ethics and dissemination: The study protocol was approved by the competent ethics committee of the Canton of Zurich (BASEC-ID 2019-00445). All acquired data will be handled according to SPHN's ethical framework for responsible data processing in personalized health research. Analyses will be performed within the secure BioMedIT environment, a national infrastructure to enable secure biomedical data processing, an integral part of SPHN. The SFNR is registered with ClinicalTrials.gov (NCT04516642), date of registration 18 August 2020 (retrospectively registered).

Article Summary

Strengths and limitations of this study

- This large multicenter study will establish a new harmonized electronic Frailty Index (eFI) from routinely collected electronic patient data at all five Swiss academic geriatric centers
- The new electronic Frailty Index (eFI) has the potential to predict two very important adverse outcomes in acute care, length of stay and in-hospital mortality
- Furthermore, these new data can be used to validate the electronic Frailty Index (eFI) against our new standardized clinical Frailty Instrument (cFI)
- Our study is not intended to establish long-term outcomes in participants identified as frail vs. their robust counterparts
- No report on potential interventions for participants identified as frail or at-risk of becoming frail is included in this study

Introduction

With the ongoing demographic transformation, aging societies convey an important challenge to present health care systems due to the growing number of older adults living with accumulating deficits, multimorbidity and frailty.[1] At the same time, health care informatics with its expanding amount of routinely collected, electronic patient data comprises a huge potential for the exploitation of data for research purposes and future developments in personalized medicine. In order to avoid age discrimination, this should also include the utilization of electronic patient data in the interest of older adults.

Over the last two decades, frailty was characterized as an age associated disproportionate decline in physiologic reserves leading to increased vulnerability to external stressors,[2] and shown to be an important predictor of negative health outcomes in older adults.[3] Nonetheless, frailty is still underdiagnosed in acute care although frail older adults have more frequent and longer hospital stays, are re-hospitalized more often and eventually die earlier than their non-frail counterparts.[3,4]

The British Geriatric Society issued a recommendation for routine frailty screening in geriatric outpatients in order to timely assess the risk of frailty on the health of older adults.[5] Moreover, frailty is becoming more and more recognized as a useful concept for risk stratification in various medical specialties, from oncology to heart surgery.[6] However, there is so far no agreement either on the ideal conceptualization of frailty or on a single best screening instrument.[7,8] This appears to be a major roadblock for the broader implementation of the frailty concept into patient care.[9] At the same time, assessing frailty systematically in clinical care might open up a window of opportunity for both improving patient care for older adults and accelerating research efforts for a better understanding of the underlying pathophysiology of the frailty syndrome.[10]

Today, among the highly cited frailty conceptualizations, the frailty phenotype by Fried et al.[11] and the deficit accumulation concept (i.e. frailty index) by Rockwood and Mitnitski et al.[12] stand out as the two most extensively investigated approaches of frailty.[13] Deriving a frailty index from electronic patient data that are routinely collected, has the potential to expedite the routine identification of frail patients in acute hospital care, as no additional resources are needed.[14]

The Swiss Frailty Network and Repository (SFNR) aims to establish a nationwide harmonized frailty index (electronic Frailty Index, eFI) consisting of 55 variables from routinely collected electronic data in patients age 65 and older collected at all five Swiss University Hospitals. A secondary validation aim investigates the performance of the eFI as a screening tool for the detection of frail

individuals identified by a harmonized clinical Frailty Instrument (cFI) based on the Fried phenotype concept, in patients age 65 and older in acute care at all five Swiss University Hospitals' Geriatric Centers. In order to take into account the importance of cognitive impairment with regard to frailty, we have added a short cognitive test as an additional component to the cFI.[15,16] We will investigate the predictive abilities of the eFI and the cFI regarding two important outcomes in acute hospital care, length of stay and in-hospital mortality. The development of a frailty data repository will in addition serve as a basic personalized health research infrastructure for future studies in older adults across all partner institutions.

The utilization of routinely collected, electronic patient data is a major focus area in health care, and of growing interest in many acute care settings, including geriatric medicine. Frailty is highly prevalent in older patients and appears as a major driver of multiple negative outcomes in this population. Establishing a harmonized electronic Frailty Index (eFI) from routinely collected electronic health care data is therefore a timely effort that will likely contribute to the improvement of care for older adult patients by early identifying those at increased risk for adverse outcomes.

The main deliverable of the SFNR will be to establish a nationwide electronic Frailty Index (eFI) derived from routinely collected electronic patient data for older adults in Switzerland curated within the SPHNs BioMedIT ecosystem. We aim to demonstrate the eFI's predictive ability for two important adverse outcomes in acute care, length of stay and in-hospital mortality and validate the eFI in the detection of frailty against our clinical Frailty-Instrument (cFI).

Addressing the topic of systematically evaluating frailty using a standardized, test-based clinical Frailty Instrument (cFI) in patients admitted to acute care at all five Swiss Academic Geriatric Centers is another important outcome of our collaboration. Therefore, establishing the SFNR will likely advance the field of geriatric medicine and research. Incorporating frailty as a criterion in acute care will allow a systematic and personalized pre-therapeutic stratification of patients according to each patient's profile. This individualized approach will enhance the definition of person-based potential harms and benefits of interventions in various medical disciplines, ranging from emergency medicine and orthogeriatric units to cardio-vascular surgery and comprehensive cancer care. We expect first results to be ready for scientific publication by mid 2022.

Methods and analysis

The SFRN is a joint effort by all five Swiss Academic Geriatric Departments (Universities of Basel, Bern, Geneva, Lausanne and Zurich and adjacent University Hospitals) that is funded by the Swiss Personalized Health Network (SPHN, Grant No. 2017DRI02), an initiative of the Swiss Federal Government, namely the State Secretariat for Education, Research and Innovation and the Federal Office of Public Health.[17]

The SFNR has five primary aims:

I. Reaching a consensus on a nationwide research reference standard to assess frailty clinically in geriatric patients at all five partner sites (definition of cFI, goal 1), see **Table 1**

II. Reaching a consensus on the candidate variables aggregating to a harmonized eFI from regularly collected electronic patient data extracted from the local clinical information systems (CIS) at all five sites (goal 2), **Table 2**

III. Setting up of a frailty data hub for the collection, organization and maintenance of coded data from all five centers including both, the cFI from patients in acute care seen by the geriatric teams at each site (related to goal 1) and the harmonized eFI (related to goal 2) from all patients age 65 and older at the partnering Swiss University Hospitals

IV. Validating the eFI as a screening tool against the cFI as a clinical criterion standard within the pooled data set from all five Geriatric Centers (validation study)

V. Investigating the predictive abilities and the correlation between the cFI and the eFI with regard to the prediction of length of stay (LOS) and in-hospital mortality in acute geriatric care (correlation study)

Sample size calculation

For the validation and correlation study, the estimated total sample size of 1,000 to 1,500 patients within a 12-month planned period was based on the two primary endpoints, hospital LOS and in-hospital mortality. In a prior study, Hope et al. found a median (IQR) LOS in the hospital for non-frail and frail individuals to be 13 (IQR 8-23) days and 17 (IQR 10-30) days, respectively.[18] Assuming symmetry, this translates to a mean (SD) of 13 (SD=(23-8)/1.35=11.1) days for non-frail individuals and 17 (14.8) days for frail individuals.[19] Another study investigating older adult medical inpatients

found a range in LOS between 4.2 and 7.8 along a Frailty Index score based on a comprehensive geriatric assessment.[20] In addition, a systematic review and meta-analysis of nine observational studies investigating outcomes in general surgery reported a mean LOS of 9.6 days (95% CI: 6.2–12.9) in frail, and 6.4 days (4.9–7.9) in non-frail patients.[21] Conservatively assuming 20% of older adults in acute care are frail (expected range from literature 20-50%)[22] and assuming a difference in hospital LOS of 4 days, a total of 418 persons (92 frail, 326 non-frail) would be needed to achieve 80% power at the 0.05 alpha level. Using a more conservative estimate of detecting a difference in hospital LOS of 2 days, 1,655 (364 frail, 1,291 non-frail) individuals would be needed to achieve 80% power at the 0.05 alpha level. Vermeiren et al. conducted a meta-analysis of 24 prospective studies comprising over 150,000 individuals and found frailty to increase the likelihood of mortality more than 2-fold (OR 2.34 [1.77-3.09]).[3] We assume 20% of individuals are frail, and leave room for a greater degree of uncertainty (wider confidence interval, CI 1.42-3.91) since this is a single study as opposed to a large meta-analysis comprising many individuals. For a mortality rate of 5% in non-frail individuals, a total of 1,077 persons (237 frail, 840 non-frail) would be required to detect an OR=2.34 at the 0.05 confidence level.

In summary, we consider a sample size of approximately 200-300 patients enrolled at each of the five partnering sites over the planned 12-month period sufficient to answer our research questions. However, the number of recruited participants at each site might not be equally distributed and differ largely due to the local environments and in-patient capacities. Of note, the primary analysis will be performed on the total sample of 1000 to 1500 patients.

Data Collection

The data collection for the components of the cFI will take place within the first four days upon admission to acute geriatric care at all partner sites by certified examiners following a standardized protocol. For calculating the eFI, only variables available from within 4 days upon admission will be retrieved from the EHR and included to the dataset.

Statistical Analysis

To evaluate the ability of the eFI screening tool to correctly classify each patient as frail, pre-frail or non-frail, we will calculate the sensitivity, specificity, as well as positive and negative predictive values of the eFI (pre-defined cut-offs and tertiles) using the cFI as our reference standard.[23] Each potential threshold will be applied to the continuous total sum scores of the eFI to classify frail vs. non-frail participants. The resulting true positive rate (sensitivity) and false positive rate (1 – specificity) will

be determined using the cFI as the reference standard. A receiver operating characteristic (ROC) curve will be constructed of all possible thresholds of the eFI. Discriminative ability will be estimated based on the area under the ROC curve and associated *C* statistics.

Hospital LOS in frail and non-frail individuals (classified by eFI and cFI) will be summarized using mean, median, standard deviation, interquartile range, minimum and maximum. Differences in hospital LOS between frail and non-frail individuals will be tested using a two-sided independent *t* test, or Mann-Whitney *U* test if the data is skewed, at the 0.05 level. In-hospital mortality rates will be calculated for the overall sample as well as for frail and non-frail subgroups. Logistic regression will be used to quantify the association of frail (vs. non-frail) on in-hospital mortality.

Progress to Date

In the first year of the project, consensus was reached among the project partners regarding the composition and scoring of the clinical frailty instrument (cFI). At the same time, the variables summarized in the electronic Frailty Index (eFI) were defined and harmonized. In the second year, the local requirements for the provision of the data to be collected were analyzed and the required IT infrastructure for secure data processing and delivery was set up. At the same time, the project-related data infrastructure within the BioMedIT network was defined and made available by SPHN. Enrolment of first participants into the study began in June 2020.

Patient and public involvement

Patients and the general public were not involved in the design, recruitment and implementation of our study. Participants will be informed regarding the detailed results of our study only upon request. However, the results will be disseminated to the public according to the SPHN's dissemination policy and by published articles.

Ethics and dissemination

For the validation study, we will use data from all patients 65 years and older recruited from acute geriatric care units who agreed to participate in the study by informed consent. For the association study, with regard to the eFI, we will use data from consecutive patients age 65 and older admitted to acute care on various departments of the partnering university hospitals from a determined starting date.

All ethics committees of the involved partner sites, chaired by the ethics committee of the Canton of Zurich have approved our study (swissethics BASEC-ID 2019-00445).

Swiss Personalized Health Network IT Ecosystem

Our project's hosting initiative, the SPHN, is currently developing a nationwide health care data ecosystem in Switzerland to work towards interoperability of data from local information systems, e.g. clinical data management systems in enabling an effective exchange of patient data (e.g. disease phenotypes) for research with the ultimate goal of advancing personalized medicine.[24,25] Our project will support and build on this effort as a driver project. In a first step, the agreed set of eFI variables was submitted to the SPHN Clinical Semantic Interoperability Working Group, which has integrated the variables in a Swiss wide core dataset and is defining for each variable in which format they shall be shared and which additional (meta-) data are needed for optimal interoperability. The data of the test-based clinical Frailty Instrument will be collected in a standardized and centralized electronic Case Report Form in REDCap (Vanderbilt University, Nashville, USA) or in the clinical information system (EHR).

Next, our collected data (eFI and cFI) will be locally pre-processed by the clinical data warehouse teams. In particular, patient IDs will be mapped and de-identified before sharing to respect data privacy regulations.[24] Additionally, a standardized format for data transfer defined by a Data Coordination Center (DCC) will be used in order to allow interoperability. We will utilize the novel Swiss BioMedIT-Node secure data infrastructure currently under development by the Swiss Institute of Bioinformatics (SIB) and managed by the Personalized Health Informatics (PHI) Group and coordinated by the DCC as part of SPHN.[26] The de-identified data will be encrypted with a secure, standard mechanism (GPG) and sent via secure transfer to BioMedIT.

On BioMedIT, the analysis of the data will take place using state of the art software and tools thereby ensuring highest security levels for access to data, processing and sharing. FAIR data

principles (findability, accessibility, interoperability, reusability) will be respected and ensured throughout the project in accordance with SPHN strategy.

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Tables and Figures

Table 1. Components of the SFNR clinical Frailty Instrument (cFI)

Domain (item)	**Operationalization** (test-based)	**Cut-Point** (threshold)
Shrinking (Weight Loss)	**Unintentional weight loss** or loss of appetite; report of lose clothing, weight loss documented in patient chart	Any reported weight loss or loss of appetite or lose clothing, or >5% last 6 months (from EHR)
Fatigue	**Self-reported exhaustion** measured by Geriatric Depression Scale 4-item	≥2 Points on GDS-4[27,28]
Slowness	**Slow gait speed** on standardized 4m measurement from a standing start (best of 2 consecutive measurements)	Gait speed below 0.8m/s
Weakness	**Low hand grip strength** measured by the Martin Vigorimeter (in Kilopascal), best of 3 consecutive trials at the dominant hand at time of assessment	Below the median of lowest 20% (by gender and age <75 and ≥75 years of age) compared to population based reference sample (from DO-HEALTH[29])
Low Activity Level	**Reported frequency of activities with moderate energy expenditure** (question BR016_ModSprtsAct from SHARE questionnaire[30])	Answer of “less than once a week”
Cognition	**Three item recall, and clock drawing test** (CDT)	Any error in recall or CDT indicates cognitive disturbance

Table 2. Variables and Coding of the SFNR electronic Frailty Index (eFI)

System	Source	Variables (No.)	Cut-point/Coding
Functional Impairments	Electronic Health Records: Electronic Nursing Charts (NANDA)	1. Chronic constipation 2. Feeling tired 3. Problems with falling/staying asleep 4. Problems with sleep-awake cycle 5. Urinary incontinence 6. Help getting on/off bed 7. Help going to the toilet 8. Help walking 9. History of falls 10. Inability to walk stairs 11. Irregular gait pattern 12. Patient using walking equipment/aid 13. Problems getting dressed 14. Problems with bathing 15. Clouding or delirium	yes=1, no=0
		16. Food intake	impaired=1, normal=0
Comorbidities	Electronic Health Records: Diagnosis List Medication Use	17. Active malignancy 18. Hearing impairment 19. History of osteoporosis 20. Cardiac arrhythmias 21. Coronary heart disease 22. Pressure sores (decubital ulcers) 23. Diabetes mellitus 24. History of seizures 25. History of stroke 26. Memory impairment 27. Chronic obstructive lung disease (COPD) 28. Use of anticoagulation medication 29. Use of antiplatelet medication 30. Polypharmacy (>5 drugs) 31. Use of sedative, hypnotic, and/or neuroleptic drugs	Presence (yes)=1, absence (no)=0
Laboratory Results	Primary Laboratory System	32. Haematocrit	<35%=1, ≥35%=0
		33. Haemoglobin 34. Platelet Count 35. Red cell volume (MCV) 36. Creatinine 37. Urea 38. Thyrotropin (TSH) 39. C-reactive protein (CRP) 40. Lymphocyte total count 41. HDL (High-density lipoprotein) 42. Potassium 43. Sodium 44. Albumin	Serum concentration above or below reference range=1, within=0
		45. Blood glucose	<3.9 or >15 mmol/l=1, other=0
		46. Cholesterol	>7 or <3.5 mmol/L=1, other=0
Vital Signs	Electronic Health Records	47. Body Temperature 48. Diastolic blood pressure 49. Heart rate (pulse) 50. Systolic blood pressure 51. Oxygen saturation (spO2) 52. Patient requires supplemental oxygen	<36,3°C=1, ≥36,3°C=0 >90mmHg=1, ≤90 mmHg=0 <60 or >99 BPM=1, other=0 >140mmHg=1, ≤140 mmHg=0 <90%=1, ≥90%=0 yes=1, no=0
Other	Electronic Health Records	53. Age 54. BMI (Body Mass Index)	>80=1, ≤80=0 <18.5 or ≥30=1; >25 and <30=0.5, other=0
		55. Patient reports being in pain	yes=1, no=0

List of Abbreviations

AUC	-	Area under the curve
BASEC	-	Business Administration System for Ethics Committees
cFI	-	clinical Frailty Instrument
CI	-	Confidence Interval
eFI	-	electronic Frailty Index
DCC	-	Data Coordination Center
EHR	-	Electronic Health Records
GPG	-	Gnu Privacy Guard
ID	-	Identifyer
IQR	-	Inter quartile range
LOS	-	Length of stay
OR	-	Odds ratio
PHI	-	Personalized Health Informatics
ROC	-	Receiver Operating Characteristics
SFNR	-	Swiss Frailty Network & Repository
SIB	-	Swiss Institute of Bioinformatics
SPHN	-	Swiss Personalized Health Network

Declarations

- *Ethics approval and consent to participate*

  The competent ethic committees of the involved partner sites, chaired by the Ethics Committee of the Canton of Zurich, Switzerland have approved our study (swissethics BASEC-ID 2019-00445, DOA September 23, 2019). Participants are enrolled to the study after written informed consent.

- *Competing interests*

  The authors declare that they have no competing interests.

- Funding

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- Authors' contributions

  MG and KE prepared the first draft of the manuscript. POCB and LAA provided the power analysis and wrote the section on statistical analysis. LSB, TM, DB, DZ, CJB, GG, RWK, AES have read and edited the paper for intellectual content and contributed significantly to the manuscript. HABF was a major contributor in writing the final manuscript. MG prepared the final editing before submission. All authors read and approved the final manuscript.

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Swiss Frailty Network & Repository – Protocol of a Swiss Personalized Health Network's Driver Project Observational Study

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Swiss Frailty Network & Repository – Protocol of a Swiss Personalized Health Network's Driver Project Observational Study

Michael Gagesch[1,2], Karin Edler[3], Patricia O. Chocano-Bedoya[2,4], Lauren A. Abderhalden[2], Laurence Seematter-Bagnoud[5], Tobias Meyer[6], Dominic Bertschi[6,7] Dina Zekry[8], Christophe J. Büla[5], Gabriel Gold[8], Reto W. Kressig[6], Andreas E. Stuck[7], and Heike A. Bischoff-Ferrari[1,2,9]

Affiliations

[1] Department of Geriatrics, University Hospital Zurich, Zurich, Switzerland
[2] Centre on Aging and Mobility, University Hospital Zurich and University of Zurich, Zurich, Switzerland
[3] Research Data Service Center, University Hospital Zurich, Zurich, Switzerland
[4] Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
[5] Service of Geriatric Medicine and Geriatric Rehabilitation, Lausanne University Hospital, Lausanne, Switzerland
[6] University Department of Geriatric Medicine FELIX PLATTER, and University of Basel, Basel, Switzerland
[7] Department of Geriatrics, Inselspital, University Hospital Bern, and University of Bern, Bern, Switzerland
[8] Department of Rehabilitation and Geriatrics, University Hospitals Geneva, Geneva, Switzerland
[9] City Hospital Waid and Triemli, Zurich, Switzerland

Corresponding Author

Michael Gagesch, MD

Dept. of Geriatrics

University Hospital Zurich

Zurich, Switzerland

Email: michael.gagesch@usz.ch

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Abstract

Introduction: Early identification of frailty by clinical instruments or accumulation of deficit indexes can contribute to improve health care for older adults, including the prevention of negative outcomes in acute care. However, conflicting evidence exists on how to best capture frailty in this setting. Simultaneously, the increasing utilization of electronic health records (EHR) opens up new possibilities for research and patient care, including frailty.

Methods and analysis: The Swiss Frailty Network and Repository (SFNR) primarily aims to develop an electronic Frailty Index (eFI) from routinely available EHR data in order to investigate its predictive value against length of stay and in-hospital mortality as two important clinical outcomes in a study sample of 1,000-1,500 hospital patients age 65 and older. In addition, we will examine the correlation between the eFI and a test-based clinical Frailty Instrument (cFI) to compare both concepts in Swiss older adults in acute care settings. As a Swiss Personalized Health Network (SPHN) driver project, our study will report on the characteristics and usability of the first nationwide eFI in Switzerland connecting all five Swiss University Hospitals' Geriatric Departments with a representative sample of patients aged 65 years and older admitted to acute care.

Ethics and dissemination: The study protocol was approved by the competent ethics committee of the Canton of Zurich (BASEC-ID 2019-00445). All acquired data will be handled according to SPHN's ethical framework for responsible data processing in personalized health research. Analyses will be performed within the secure BioMedIT environment, a national infrastructure to enable secure biomedical data processing, an integral part of SPHN. The SFNR is registered with ClinicalTrials.gov (NCT04516642), date of registration 18 August 2020 (retrospectively registered).

Article Summary

Strengths and limitations of this study

- This large multicenter study, recruiting 1,000-1,500 individuals will establish a new harmonized electronic Frailty Index (eFI) from routinely collected electronic patient data at all five Swiss academic geriatric centers
- The new electronic Frailty Index (eFI) has the potential to predict two very important adverse outcomes in acute care, length of stay and in-hospital mortality
- Furthermore, these new data will be used to investigate the correlation between the electronic Frailty Index (eFI) and a standardized clinical Frailty Instrument (cFI)
- Our study is not intended to establish long-term outcomes in participants identified as frail vs. their robust counterparts
- No report on potential interventions for participants identified as frail or at-risk of becoming frail is included at this stage of the project, however we aim to lay groundwork for a future implementation of frailty screening in clinical care

Introduction

With the ongoing demographic transformation, aging societies convey an important challenge to present health care systems due to the growing number of older adults living with accumulating deficits, multimorbidity and frailty.[1] At the same time, health care informatics with its expanding amount of routinely collected, electronic patient data comprises a huge potential for the exploitation of data for research purposes and future developments in personalized medicine. In order to avoid age discrimination, this should also include the utilization of electronic patient data in the interest of older adults.

Over the last two decades, frailty was characterized as an age associated disproportionate decline in physiologic reserves leading to increased vulnerability to external stressors,[2] and shown to be an important predictor of negative health outcomes in older adults.[3] Nonetheless, frailty is still underdiagnosed in acute care although frail older adults have more frequent and longer hospital stays, are re-hospitalized more often and eventually die earlier than their non-frail counterparts.[3,4]

The British Geriatric Society issued a recommendation for routine frailty screening in geriatric outpatients in order to timely assess the risk of frailty on the health of older adults.[5] Moreover, frailty is becoming more and more recognized as a useful concept for risk stratification in various medical specialties, from oncology to heart surgery.[6] However, as the field is evolving, there has been no agreement either on the ideal conceptualization of frailty or on a single best screening instrument over the past decades.[7-10] This happened to be a major roadblock for the broader implementation of the frailty concept into patient care.[11] At the same time, assessing frailty systematically in clinical care might open up a window of opportunity for both improving patient care for older adults and accelerating research efforts for a better understanding of the underlying pathophysiology of frailty as a state or condition (i.e. by a Frailty Index approach) and as a syndrome (i.e. the frailty phenotype).[10]

Today, among the highly cited frailty conceptualizations, the frailty phenotype by Fried et al.[12] and the deficit accumulation concept (i.e. Frailty Index) by Rockwood and Mitnitski et al.[13] stand out as the two most extensively investigated approaches of frailty.[14] As this two approaches measure different concepts of frailty (i.e. a clinical syndrome vs. a multi-system decline based index) their comparability may be limited. In addition, it should be taken into account that the phenotype usually requires clinical measurements, whereas a Frailty Index (FI) can be generated from available patient data collected during routine clinical practice. Therefore, deriving a FI from electronic health records (EHR) data that are routinely collected, has the potential to expedite the routine identification of frail

patients in acute hospital care in various medical specialties, as no additional resources are needed.[15] This approach has been recently demonstrated by Cesari et al. investigating a FI in an Italian cohort of hospitalized patients.[16] With regard to the investigation of significant clinical endpoints including in-hospital mortality and length of stay by an electronic Frailty Index (eFI), which has not been undertaken in hospitalized older adults in Switzerland so far, a comparative view on both frailty concepts contains the opportunity to provide important additional information.

The Swiss Frailty Network and Repository (SFNR) aims to establish a nationwide harmonized eFI consisting of 55 variables from routinely collected EHR data in patients age 65 and older at all five Swiss University Hospitals in order to investigate its predictive abilities in regard to length of stay and in-hospital mortality. A secondary validation aim investigates the correlation of the eFI as a screening tool against the detection of frailty by a harmonized clinical Frailty Instrument (cFI) based on the Fried phenotype concept, in a subset of patients age 65 and older from acute geriatric care at all five Swiss University Hospitals' Geriatric Centers. In order to take into account the importance of cognitive impairment with regard to frailty, we have added a short cognitive test as an additional component to the cFI.[17,18] We will investigate the predictive abilities of both, the eFI and the cFI regarding two important outcomes in acute hospital care, length of stay and in-hospital mortality. The development of a frailty data repository will in addition serve as a basic personalized health research infrastructure for future studies in older adults across all partner institutions.

The utilization of routinely collected, electronic patient data is a major focus area in health care, and of growing interest in many acute care settings, including geriatric medicine. Frailty is highly prevalent in older patients and appears as a major driver of multiple negative outcomes in this population. Establishing a harmonized eFI from routinely collected EHR data is therefore a timely effort that will likely contribute to the improvement of care for older adult patients by early identifying those at increased risk for adverse outcomes.

The main deliverable of the SFNR will be to establish a nationwide eFI derived from routinely collected electronic patient data for older adults in Switzerland curated within the SPHNs BioMedIT ecosystem. We aim to demonstrate the eFI's predictive ability for length of stay and in-hospital mortality and investigate the comparative performance of the eFI in the detection of frailty against our clinical Frailty-Instrument (cFI) in a subset of patients admitted to acute geriatric care.

Our proposition of a systematic clinical evaluation of frailty using the cFI as a clinical research reference standard in all enrolled patients admitted to acute geriatric care at all five Swiss Academic

Geriatric Centers is a secondary outcome of our collaboration that may lead to a more unified approach to the measurement of the frailty phenotype on the national level. Therefore, establishing the SFNR will likely advance both, the field of geriatric medicine and research in Switzerland. Incorporating frailty as a criterion in acute care will allow a systematic and personalized pre-therapeutic stratification of patients according to each patient's profile. This individualized approach will enhance the definition of person-based potential harms and benefits of interventions in various medical disciplines, ranging from emergency medicine and orthogeriatric units to cardio-vascular surgery and comprehensive cancer care. We expect first results to be ready for scientific publication by mid 2022.

Methods and analysis

The SFRN is a joint effort by all five Swiss Academic Geriatric Departments (Universities of Basel, Bern, Geneva, Lausanne and Zurich and adjacent University Hospitals) that is funded by the Swiss Personalized Health Network (SPHN, Grant No. 2017DRI02), an initiative of the Swiss Federal Government, namely the State Secretariat for Education, Research and Innovation and the Federal Office of Public Health.[19]

The SFNR has five primary aims:

I. Reaching a consensus on a nationwide research reference standard to assess frailty clinically in geriatric patients at all five partner sites (definition of cFI, goal 1), see **Table 1**

II. Reaching a consensus on the candidate variables aggregating to a harmonized eFI from regularly collected electronic patient data extracted from the local clinical information systems (CIS) at all five sites (goal 2), **Table 2**

III. Setting up of a frailty data hub for the collection, organization and maintenance of coded data from all five centers including both, the cFI from patients in acute care seen by the geriatric teams at each site (related to goal 1) and the harmonized eFI (related to goal 2) from all patients age 65 and older at the partnering Swiss University Hospitals

IV. Investigating the correlation of the eFI as a screening tool against the cFI as a clinical criterion standard within the pooled data set from all five Geriatric Centers (association study)

V. Investigating whether the prognostic abilities differ between the cFI and the eFI with regard to the prediction of length of stay (LOS) and in-hospital mortality in acute geriatric care (correlation study)

Sample size calculation

For our study, the estimated total sample size of 1,000 to 1,500 patients within a 12-month planned period was based on the two primary endpoints, hospital LOS and in-hospital mortality. In a prior study, Hope et al. found a median (IQR) LOS in the hospital for non-frail and frail individuals to be 13 (IQR 8-23) days and 17 (IQR 10-30) days, respectively.[20] Assuming symmetry, this translates to a mean (SD) of 13 (SD=(23-8)/1.35=11.1) days for non-frail individuals and 17 (14.8) days for frail

individuals.[21] Another study investigating older adult medical inpatients found a range in LOS between 4.2 and 7.8 along a Frailty Index score based on a comprehensive geriatric assessment.[22] In addition, a systematic review and meta-analysis of nine observational studies investigating outcomes in general surgery reported a mean LOS of 9.6 days (95% CI: 6.2–12.9) in frail, and 6.4 days (4.9–7.9) in non-frail patients.[23] Conservatively assuming 20% of older adults in acute care are frail (expected range from literature 20-50%)[24] and assuming a difference in hospital LOS of 4 days, a total of 418 persons (92 frail, 326 non-frail) would be needed to achieve 80% power at the 0.05 alpha level. Using a more conservative estimate of detecting a difference in hospital LOS of 2 days, 1,655 (364 frail, 1,291 non-frail) individuals would be needed to achieve 80% power at the 0.05 alpha level. Vermeiren et al. conducted a meta-analysis of 24 prospective studies comprising over 150,000 individuals and found frailty to increase the likelihood of mortality more than 2-fold (OR 2.34 [1.77-3.09]).[3] We assume 20% of individuals are frail, and leave room for a greater degree of uncertainty (wider confidence interval, CI 1.42-3.91) since this is a single study as opposed to a large meta-analysis comprising many individuals. For a mortality rate of 5% in non-frail individuals, a total of 1,077 persons (237 frail, 840 non-frail) would be required to detect an OR=2.34 at the 0.05 confidence level.

In summary, we consider a sample size of approximately 200-300 patients enrolled at each of the five partnering sites over the planned 12-month period sufficient to answer our research questions. However, the number of recruited participants at each site might not be equally distributed and differ largely due to the local environments and in-patient capacities. Of note, the primary analysis will be performed on the total sample of 1000 to 1500 patients.

Data Collection

The data collection for the components of the cFI will take place within the first four days upon admission to acute geriatric care at all partner sites by certified examiners following a standardized protocol. For calculating the eFI, only variables available from within 4 days upon admission will be retrieved from the EHR and included to the dataset.

Statistical Analysis

In regard to the eFI's variables, each will be scored as either "1", i.e. presence of the deficit or "0", i.e. absence of the deficit, except for Body Mass Index (BMI, <18.5 or ≥30 = 1, >25 and <30 = 0.5, other = 0), see table 2 for full list of variables. We will use validated cut-points regarding the classification of the degree of robustness or frailty from prior literature.[25,26] We will additionally test, whether eFI scores differ between the classification of frail/pre-frail and robust by the cFI in our sub-

sample from acute geriatric care. To evaluate the ability of the eFI screening tool to correctly classify each patient as frail, pre-frail or non-frail in regard to the phenotypic approach, we will calculate the sensitivity, specificity, as well as positive and negative predictive values of the eFI (pre-defined cut-offs and tertiles) against the cFI.[27] Each potential threshold will be applied to the continuous total sum scores of the eFI to classify frail vs. non-frail participants. The resulting true positive rate (sensitivity) and false positive rate (1 – specificity) will be determined using the cFI as the reference. A receiver operating characteristic (ROC) curve will be constructed of all possible thresholds of the eFI. Discriminative ability will be estimated based on the area under the ROC curve and associated *C* statistics.

Hospital LOS in frail and non-frail individuals (classified by eFI and cFI) will be summarized using mean, median, standard deviation, interquartile range, minimum and maximum. Differences in hospital LOS between frail and non-frail individuals will be tested using a two-sided independent *t* test, or Mann-Whitney *U* test if the data is skewed, at the 0.05 level. In-hospital mortality rates will be calculated for the overall sample as well as for frail and non-frail subgroups. Logistic regression will be used to quantify the association of frail (vs. non-frail) on in-hospital mortality.

Progress to Date

In the first year of the project, consensus was reached among the project partners regarding the composition and scoring of the clinical frailty instrument (cFI). At the same time, the 55 variables summarized in the electronic Frailty Index (eFI) were defined and harmonized. In the second year, the local requirements for the provision of the data to be collected were analyzed and the required IT infrastructure for secure data processing and delivery was set up. At the same time, the project-related data infrastructure within the BioMedIT network was defined and made available by SPHN. Enrolment of first participants into the study began in June 2020.

Patient and public involvement

Patients and the general public were not involved in the design, recruitment and implementation of our study. Participants will be informed regarding the detailed results of our study only upon request. However, the results will be disseminated to the public according to the SPHN's dissemination policy and by published articles.

Ethics and dissemination

For the association study, with regard to the eFI, we will use data from consecutive patients age 65 and older admitted to acute care on various departments of the partnering university hospitals from a determined starting date and with available written informed consent for further use of routine clinical data. For the correlation study, we will use data from all patients 65 years and older recruited from acute geriatric care units who agreed to participate in the study by informed consent.

All ethics committees of the involved partner sites, chaired by the ethics committee of the Canton of Zurich have approved our study (swissethics BASEC-ID 2019-00445).

Swiss Personalized Health Network IT Ecosystem

Our project's hosting initiative, the SPHN, is currently developing a nationwide health care data ecosystem in Switzerland to work towards interoperability of data from local information systems, e.g. clinical data management systems in enabling an effective exchange of patient data (e.g. disease phenotypes) for research with the ultimate goal of advancing personalized medicine.[28,29] Our project will support and build on this effort as a driver project. In a first step, the agreed set of eFI variables was submitted to the SPHN Clinical Semantic Interoperability Working Group, which has integrated the variables in a Swiss wide core dataset and is defining for each variable in which format they shall be shared and which additional (meta-) data are needed for optimal interoperability. The data of the test-based clinical Frailty Instrument will be collected in a standardized and centralized electronic Case Report Form in REDCap (Vanderbilt University, Nashville, USA) or in the clinical information system (EHR).

Next, our collected data (eFI and cFI) will be locally pre-processed by the clinical data warehouse teams. In particular, patient IDs will be mapped and de-identified before sharing to respect data privacy regulations.[28] Additionally, a standardized format for data transfer defined by a Data Coordination Center (DCC) will be used in order to allow interoperability. We will utilize the novel Swiss BioMedIT-Node secure data infrastructure currently under development by the Swiss Institute of Bioinformatics (SIB) and managed by the Personalized Health Informatics (PHI) Group and coordinated by the DCC as part of SPHN.[30] The de-identified data will be encrypted with a secure, standard mechanism (GPG) and sent via secure transfer to BioMedIT.

On BioMedIT, the analysis of the data will take place using state of the art software and tools thereby ensuring highest security levels for access to data, processing and sharing. FAIR data

principles (findability, accessibility, interoperability, reusability) will be respected and ensured throughout the project in accordance with SPHN strategy.

Tables and Figures

Table 1. Components of the SFNR clinical Frailty Instrument (cFI)

Domain (item)	**Operationalization** (test-based)	**Cut-Point** (threshold)
Shrinking (Weight Loss)	**Unintentional weight loss** or loss of appetite; report of lose clothing, weight loss documented in patient chart	Any reported weight loss or loss of appetite or lose clothing, or >5% last 6 months (from EHR)
Fatigue	**Self-reported exhaustion** measured by Geriatric Depression Scale 4-item	≥2 Points on GDS-4[31,32]
Slowness	**Slow gait speed** on standardized 4m measurement from a standing start (best of 2 consecutive measurements)	Gait speed below 0.8m/s
Weakness	**Low hand grip strength** measured by the Martin Vigorimeter (in Kilopascal), best of 3 consecutive trials at the dominant hand at time of assessment	Below the median of lowest 20% (by gender and age <75 and ≥75 years of age) compared to a sample of generally healthy Swiss older adults (from the DO-HEALTH study[33,34])
Low Activity Level	**Reported frequency of activities with moderate energy expenditure** (question BR016_ModSprtsAct from SHARE questionnaire[35])	Answer of “less than once a week”
Cognition	**Three item recall, and clock drawing test** (CDT)	Any error in recall or CDT indicates cognitive disturbance

Table 2. Variables and Coding of the SFNR electronic Frailty Index (eFI)

System	Source	Variables (No.)	Cut-point/Coding
Functional Impairments	Electronic Health Records: Electronic Nursing Charts (NANDA)	1. Chronic constipation 2. Feeling tired 3. Problems with falling/staying asleep 4. Problems with sleep-awake cycle 5. Urinary incontinence 6. Help getting on/off bed 7. Help going to the toilet 8. Help walking 9. History of falls 10. Inability to walk stairs 11. Irregular gait pattern 12. Patient using walking equipment/aid 13. Problems getting dressed 14. Problems with bathing 15. Clouding or delirium	yes=1, no=0
		16. Food intake	impaired=1, normal=0
Comorbidities	Electronic Health Records: Diagnosis List Medication Use	17. Active malignancy 18. Hearing impairment 19. History of osteoporosis 20. Cardiac arrhythmias 21. Coronary heart disease 22. Pressure sores (decubital ulcers) 23. Diabetes mellitus 24. History of seizures 25. History of stroke 26. Memory impairment 27. Chronic obstructive lung disease (COPD) 28. Use of anticoagulation medication 29. Use of antiplatelet medication 30. Polypharmacy (>5 drugs) 31. Use of sedative, hypnotic, and/or neuroleptic drugs	Presence (yes)=1, absence (no)=0
Laboratory Results	Primary Laboratory System	32. Haematocrit	<35%=1, ≥35%=0
		33. Haemoglobin 34. Platelet Count 35. Red cell volume (MCV) 36. Creatinine 37. Urea 38. Thyrotropin (TSH) 39. C-reactive protein (CRP) 40. Lymphocyte total count 41. HDL (High-density lipoprotein) 42. Potassium 43. Sodium 44. Albumin	Serum concentration above or below reference range=1, within=0
		45. Blood glucose	<3.9 or >15 mmol/l=1, other=0
		46. Cholesterol	>7 or <3.5 mmol/L=1, other=0
Vital Signs	Electronic Health Records	47. Body Temperature 48. Diastolic blood pressure 49. Heart rate (pulse) 50. Systolic blood pressure 51. Oxygen saturation (spO2) 52. Patient requires supplemental oxygen	<36,3°C=1, ≥36,3°C=0 >90mmHg=1, ≤90 mmHg=0 <60 or >99 BPM=1, other=0 >140mmHg=1, ≤140 mmHg=0 <90%=1, ≥90%=0 yes=1, no=0
Other	Electronic Health Records	53. Age 54. BMI (Body Mass Index)	>80=1, ≤80=0 <18.5 or ≥30=1; >25 and <30=0.5, other=0
		55. Patient reports being in pain	yes=1, no=0

List of Abbreviations

AUC	-	Area under the curve
BASEC	-	Business Administration System for Ethics Committees
cFI	-	clinical Frailty Instrument
CI	-	Confidence Interval
eFI	-	electronic Frailty Index
DCC	-	Data Coordination Center
EHR	-	Electronic Health Records
GPG	-	Gnu Privacy Guard
ID	-	Identifyer
IQR	-	Inter quartile range
LOS	-	Length of stay
OR	-	Odds ratio
PHI	-	Personalized Health Informatics
ROC	-	Receiver Operating Characteristics
SFNR	-	Swiss Frailty Network & Repository
SIB	-	Swiss Institute of Bioinformatics
SPHN	-	Swiss Personalized Health Network

Declarations

- *Ethics approval and consent to participate*

  The competent ethic committees of the involved partner sites, chaired by the Ethics Committee of the Canton of Zurich, Switzerland have approved our study (swissethics BASEC-ID 2019-00445, DOA September 23, 2019). Participants are enrolled to the study after written informed consent.

- *Competing interests*

  The authors declare that they have no competing interests.

- Funding

  This project has been funded as a driver project by the Swiss Personalized Health Network (grant number 2017DRI02) with the participating University Hospitals in-kind contributions of

the same amount (matching funds, grant number N/A). The funding source was not involved in study design, and will not be involved in the collection, analysis or interpretation of data.

- Authors' contributions

MG and KE prepared the first draft of the manuscript. POCB and LAA provided the power analysis and wrote the section on statistical analysis. LSB, TM, DB, DZ, CJB, GG, RWK, AES have read and edited the paper for intellectual content and contributed significantly to the manuscript. HABF was a major contributor in writing the final manuscript. MG prepared the final editing before submission. All authors read and approved the final manuscript.

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