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Highlighting the Impact of Health-Related Quality of Life in Older Inpatients

The chance of patient-reported outcomes for the turnaround to a resource-orientated treatment

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Annika Franziska Bausch, geb. Heeß
aus Backnang

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Dekan: Universitätsprofessor Dr. med. G. R. Fink
1. Gutachterin: Universitätsprofessorin Dr. med. Dr. M. C. Polidori- Nelles
2. Gutachterin: Professorin Dr. rer. medic N. Scholten

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Die Entwicklung der zugrundeliegenden prospektiven Studie erfolgte durch mich in Zusammenarbeit mit Frau Prof. Priv.-Doz. Dr. Dr. M. Cristina Polidori-Nelles, Leiterin des Schwerpunkts für Klinische Altersforschung der Klinik II für Innere Medizin der Uniklinik Köln, Köln, Deutschland, sowie Dr. med. Anna Maria Affeldt (geb. Meyer) und Dr. med. Lena Pickert, Doktorandinnen im Schwerpunkt Klinische Altersforschung der Klinik II für Innere Medizin der Uniklinik Köln, Köln, Deutschland. Die statistische Beratung zur Studie erfolgte durch Frau Ingrid Becker vom Institut für Medizinische Statistik und Bioinformatik der Uniklinik Köln, Köln, Deutschland.

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List of Abbreviations

QoL: Quality of life

HRQoL: Health-related quality of life

CGA: Comprehensive Geriatric Assessment

MPI: Multidimensional Prognostic Index

MPI-InGAH: Multidimensional Prognostic Index – Influence of Geriatric Assessment on Hospitalisation of Older, Multimorbid Patients

GR: geriatric resource(s)

GS: geriatric syndrome(s)

ADL: Activities of Daily Living

IADL: Instrumental Activities of Daily Living

MNA-SF: Mini Nutritional Assessment – Short Form

ESS: Exton Smith Scale

SPMSQ: Short Portable Mental Status Questionnaire

CIRS-CI: Cumulative Illness Rating Scale – Comorbidity Index

LHS: Length of Hospital Stay

FORTA: Fit for the Aged

START: Screening Tool to Alert Doctors to start the Right Treatment

STOPP: Screening Tool of Older Persons' Prescriptions

WHO: World Health Organization

1. Summary

A patient's quality of life has become increasingly important as a relevant outcome in recent years. Despite evolutions in the medical outcome culture, the structured and comparable recording of quality of life remains difficult [1]. The large number of patient-reported outcome measurement instruments is often based on different definitions of quality of life. In medicine, often, health-related quality of life (HRQoL) is to be mapped, but authors seldomly differ between both terms. In this paper, HRQoL will be highlighted, and the problem of measurability will be taken into account by using an established measurement instrument, the EQ-5D, and a simple subjective numerical scale.

This dissertation is intended to identify and critically discuss the interrelation between quality of life and geriatric conditions. For this purpose, 165 patients older than 65 years on the nephrology ward of the University Hospital of Cologne were included in the study. A Comprehensive Geriatric Assessment (CGA) was carried out using the Multidimensional Prognostic Index (MPI), and geriatric syndromes and resources as well as HRQoL were also recorded. After discharge, the patients were followed up by telephone after 3, 6 and 12 months and asked about their health status and quality of life.

The study population consisted of 60% of men; the average age was 76 years. The majority of the patients were pre-frail, corresponding to the MPI-2 group, whereas 20% were frail (MPI-3). HRQoL was independent of age, gender, education and living conditions, but the regression model showed significant associations with MPI and the number of Geriatric Syndromes (GS) and resources (GR), the latter also after adjustment for age, gender and MPI-group. A further regression analysis identified immobility, depression, chronic pain, fluid disorders and electrolyte balance and swallowing disorders as well as emotional and motivational resources as significant factors influencing HRQoL.

Follow-up results were obtained for 126 patients. Significant correlations were found between survival and MPI, number of GR and GS and HRQoL. Furthermore, MPI and number of GR and GS correlated with HRQoL in the 6- and 12-month follow-up.

The increasing relevance of patient-centred outcomes such as quality of life can be confirmed by the present results. The close associations between CGA, prognosis and quality of life call for future surveys to place subjective measures and individual assessments and resources at the centre of research and include those in future treatment planning.

1.1 Deutsche Zusammenfassung

Die Lebensqualität eines Patienten hat in den letzten Jahren zunehmend an Bedeutung gewonnen. Trotz der Umbrüche in der medizinischen Outcome-Kultur gestaltet sich die strukturierte und vergleichbare Erfassung von Lebensqualität weiterhin schwierig [1]. Die Vielzahl an Messinstrumenten des patient-reported Outcomes Lebensqualität basiert oft auf unterschiedlichen Definitionen von Lebensqualität, mitunter auch, da in der Medizin häufig die gesundheitsbezogene Lebensqualität (HRQoL) abgebildet werden soll. Auch im vorliegenden Paper soll die gesundheitsbezogene Lebensqualität dargestellt werden und der Problematik der Messbarkeit insofern Rechnung getragen werden, als dass ein etabliertes Messinstrument, der EQ-5D und eine einfache subjektive numerische Skala verwendet werden. Die vorliegende Doktorarbeit soll das Spannungsfeld von Lebensqualität und geriatrischen Gegebenheiten benennen und kritisch diskutieren. Hierfür wurden 165 Patienten älter als 65 Jahre auf der nephrologischen Normalstation der Universitätsklinik Köln in die Studie eingeschlossen. Mit jedem Patienten wurde ein Comprehensive Geriatric Assessment (CGA) mittels des Multidimensionalen Prognostischen Index (MPI) durchgeführt, es erfolgte zusätzlich die Erfassung von Geriatrischen Syndromen und Ressourcen sowie der gesundheitsbezogenen Lebensqualität. Nach Entlassung wurden die Patienten nach 3, 6 und 12 Monaten telefonisch nachverfolgt und zu ihrem Gesundheitsstatus und der Lebensqualität befragt.

Die Studienpopulation bestand zu 60% aus Männern, das Durchschnittsalter betrug 76 Jahre. Der Hauptteil der Patienten war pre-frail, entsprechend er MPI-2 Gruppe, 20% waren frail (MPI-3). Die gesundheitsbezogene Lebensqualität zeigte sich nicht assoziiert mit Alter, Geschlecht, Ausbildung und Lebensumständen, jedoch zeigten sich im Regressionsmodel signifikante Assoziationen zum MPI und zur Anzahl an Geriatrischen Syndromen (GS) und Ressourcen (GR), letzte auch nach Adjustierung für Alter, Geschlecht und MPI-Risikogruppe. Eine weitere Regressionsanalyse konnte Immobilität, Depression, chronische Schmerzen, Störungen im Flüssigkeits- und Elektrolythaushalt und Schluckstörungen sowie emotionale und motivationale Ressourcen als signifikante Einflussgrößen auf die HRQoL identifizieren.

Die Follow-Up Ergebnisse konnten für 126 Patienten erhoben werden. Hierbei zeigten sich signifikante Korrelationen zwischen Überleben und MPI, Anzahl GR und GS und HRQoL. Des Weiteren korrelierten MPI und Anzahl GR und GS mit der HRQoL im 6- und 12-Monats Follow-Up.

Die zunehmende Relevanz von patientenzentrierten Outcomes wie der Lebensqualität lässt sich durch die vorliegenden Ergebnisse bestätigen. Die engen Assoziationen zwischen dem CGA, der Prognose und der Lebensqualität fordern für künftige Erhebungen, dass subjektive Maße und individuelle Bewertungen und Ressourcen in den Mittelpunkt der Forschung gerückt und in künftige Therapieplanungen einbezogen werden müssen.

2. Introduction

The quality of life of geriatric persons has gained importance in the medical research field in recent decades amongst others because of the demographic shift of the German population. Given the increasingly growing group of older citizens (the age group studied here being >65 years), chronic conditions become an urgent challenge for patient care [2]. The focus in treating multimorbid patients is rather on recognising and addressing complex geriatric patterns, which can be captured in a structured manner through a Comprehensive Geriatric Assessment [3]. Thus, the focus is shifting away from disease-inert specifics and toward a multidimensional view of the person in his or her physical, psychological and social structure. Similarly, individual organic diseases are less often the cause of hospitalizations, but rather the general loss of functionality and thus an increased risk of poor outcomes [4]. In turn, patient-centred outcomes such as quality of life and healthy life years are central to treatment planning as a goal of treatment [4].

2.1 Geriatric medicine

Medical practice underwent immense changes in the last decades. Due to advanced knowledge, new medication opportunities and technical progress, treatment strategies of several diseases improved rapidly. The achievements of modern medicine consecutively led to a shift from infectious diseases, which were a major factor of people's mortality, to an increasement of the chronically ill. Especially in older age, chronic diseases and the loss of functional reserves are common health limitations [5]. The physiological progress of declining organ functions leads to a varied and multidimensional presentation of geriatric patients.

Traditional medicine is limited regarding the heterogeneity of presented health problems in older age. In geriatric patients, a bundle of specific diseases often cannot explain the resulting heterogeneity of health phenotypes [6]. Medical approaches based on treatment of specific diseases therefore seem to be not productive in improving medical outcomes in geriatric or multimorbid patients [7]. Even recognising multimorbidity as a multiplication of several diseases does not capture the complexity of geriatric conditions. The crucial point in geriatric medicine seems to lie beyond illness and rather in a patient's functional status, which is a powerful predictive marker for adverse health outcomes independent of comorbidities [6].

In addition to complex disease and functioning models, geriatric patients differ in appointed symptoms [5], as they often present atypical symptoms like, e.g., gastrointestinal disorders in pneumonia or delirium in urinary tract infections. Other symptoms like dizziness, fatigue and pain may appear without any obvious clinical cause. Those symptoms are rather a consequence of a plurality of chronic or acute conditions [8]. Improvement of appointed

outcomes like health, functional independency and quality of life therefore cannot be reached by traditional treatment of single diseases [7].

Addressing this lack of treatment strategies, modern geriatric medicine is based on a biopsychosocial and multidimensional approach that includes physical, mental, social, cognitive and environmental factors [5]. Conducting geriatric medicine, a multi-professional and interdisciplinary team is needed – the so-called geriatric team: Physicians are necessary for medical treatment of presented acute and chronic diseases, nursing staff in collaboration with physiotherapy helps maintain mobility and functional status and occupational therapists train challenges of daily routine, mental capacities and personal hygiene. Logopaedics screen for dysphagia and social service advises patients and their relatives in providing aids [5].

The geriatric team aims to focus on intrinsic capacities of a patient. In collegial discussion, each specialist supports with his expertise and therefore improves diverse outcomes[9]. The implementation of a geriatric team leads to improved health outcomes and higher quality of life [10], reduced mortality [11] as well as economic outcomes like reduced costs [12,13] and less rehospitalisations [11].

Regarding results of a Comprehensive Geriatric Assessments, especially patients with medium or high risk for negative outcomes benefit from a geriatric treatment by improving their multidimensional prognosis [14].

2.1.1. The geriatric patient

Treatment of geriatric patients has peculiarities due to geriatric characteristics as described in the chapter above. The definition of a geriatric patient is appointed by the Deutsche Gesellschaft für Geriatrie and Deutsche Gesellschaft für Gerontologie und Geriatrie in cooperation with the Bundesarbeitsgemeinschaft Geriatrischer Einrichtungen as follows: someone presenting with geriatric-typical multimorbidity in mostly higher age (about >70 years) or someone with elevated vulnerability (80 years or older) due to loss of autonomy or risk of chronic conditions and complications [15].

According to that definition, the focus in geriatric medicine is clearly not only on age but on complexity of multimorbidity and vulnerability and resulting need of specific treatment [16].

In older age, several changes in physiology lead to higher susceptibility for adverse outcomes. Often, the reasons for hospitalisation, for example, are not attributed to a single main diagnosis [4].

Many diseases occur more often in older age like decline in visceral function [17]. Furthermore, adverse events after interventions are more likely due to age-related changes and frailty [18]. Higher vulnerability can lead to the so-called ‘geriatric cascade’, a downward spiral from lighter symptoms via complications to unfavourable outcomes and death at its end. Examples might be the cascade from dehydration to uroseptic shock or light fever to delirium [2].

Prevention of the vicious cycles by using resilience factors and giving attendance to geriatric syndromes is therefore a core focus of geriatric expertise [2].

Treatment strategies may therefore not focus on specific diseases but should be personalised and attend functioning aspects, autonomy and rehabilitation [4,19]. A helpful tool for documentation of functional status is the international classification of functioning (ICF), which may identify and highlight disability, functional disorders and environmental factors [4,20].

2.1.2. Multimorbidity

Regarding the definition of a geriatric patient, multimorbidity seems to be a main feature. The World Health Organization defined multimorbidity as the co-occurrence of two or more chronic conditions [21].

The prevalence in the older population is somewhere between 55 and 98%, depending on the underlying definition [22,23]. In Germany, people aged 80 years or older have on average 3.6 diseases [24].

However, structured reviews show that authors and even reviewers are using several different definitions of multimorbidity in their studies. The most common count of diseases was, according to the WHO, two or more [25], whereas many authors simply use the terms “several” and “multiple” conditions [26–28]. The German “DEGAM Leitlinie S3: Multimorbidität” counts patients as belonging to the multimorbid population who have three or more chronic diseases under medical attention. The reason for their definition is argued by the fact that in some countries, more than 85% of patients are multimorbid, which leads the WHO definition ad absurdum [29]. Furthermore, the WHO definition remains unclear whether an acute condition is counted among multimorbidity and whether the duration of a condition and its severity should be included.

Le Reste et al. tried to evolve a comprehensive definition of multimorbidity in order to address the above-mentioned deficits in actual definitions. In their opinion, not only diseases but also biopsychosocial factors and risk factors contribute to multimorbidity. Those thoughts and the involvement of undefined aspects led to the following comprehensive definition: “Multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor” [30]. The effects of multimorbidity are therefore modified by negative impacts like risk factors and disease burden as well as by positive factors like a good biopsychosocial condition with a social network and coping strategies [30].

The results regarding outcomes of multimorbidity are more consistent, as several studies show associations to negative health outcomes: Patients with multimorbidity are more likely disabled or frail, have worse quality of life and life satisfaction and less autonomy and functionality.

Furthermore, such patients use up more medical resources and care provisions and have a higher mortality [21,23,24,30–33].

The clinical presentation of a multimorbid patient often cannot be subsumed under a phenotype of a particular disease; multimorbidity may therefore impede an accurate assessment due to higher complexity and furthermore prescription of multiple, potentially interacting medication [26,27]. Some authors declare characteristics of multimorbidity, which include e.g. immobility, sensorial impairments, frailty and chronic pain [17]. The overlap to geriatric syndromes underlines the importance of a Comprehensive Geriatric Assessment in multimorbid patients. Since such clinical manifestations are consequence of multiple conditions, the focus must be moved from a disease-specific to a comprehensive point of view [8,34].
Due to a lack of standardised methods and heterogeneous results, there is less evidence regarding multimorbidity, and existing studies cannot be compared well [29]. Nevertheless, care of older people must be improved by evidence, which is proved on multimorbid patients [34]. There is a critical need of standardised studies on multimorbidity and, in consequence, on its treatment strategies.

2.1.3. The concept of frailty

Higher vulnerability and decline in autonomy seem to be crucial changes in older age as mentioned before, when discussing characteristics of a geriatric patient.
Frailty incorporates such a condition in which an individual is affected by a decline of resources and reduction of physical and mental functioning. Frail persons therefore have an elevated vulnerability for stressors [35,36].
Decompensation of a patient who is normally able to maintain daily activities can take place by exposure to even minor challenges [37], and the risk of adverse outcomes and despaired functionality rises exponentially [35].
Frailty is not a consequence of normal ageing processes but rather an extreme consequence or pathologic development of age [38]. There are many factors influencing the multidimensional concept of frailty, physical and psychosocial decline, in particular [38] as well as comorbidity [39]. Comorbidity and health problems are important factors [27]; however, frailty is not equitable to multimorbidity, as it may even be independent from type and number of preconditions [40].
Hazzard et al. restate the condition of being at risk as a disturbed balance between physiology and experienced challenges. A lack or decrease of homeostasis in different organ systems may explain the susceptibility to stressors and the subsequent, in part enormous decline [37]. Hence, they underline the high dynamic and multidimensionality of frailty and geriatric care.
The challenges of frailty research are the plurality of combinations and the various degrees in which important organ systems may be affected by the downward frailty cascade [41].

Different models have been established over time in order to identify frail elders. The “frailty phenotype”, developed by Fried et al. in 2001, was one of the first approaches to define frail persons, including five physical components that are present in the syndrome of frailty: Unintentional weight loss, self-reported exhaustion, weakness (measured by grip strength), slow walking speed and low physical activity [39]. This very simple classification diagnoses frailty if three or more criteria are present. Pre-frailty is classified by only one or two conditions given. Only if no components are applied, a person is stated robust [39].

Another approach especially addressing frailty’s multidimensional nature is the “frailty index”, developed by Rockwood and Mitniski in 2007. It is a model of multiple health deficits, which accumulate in a clinical frailty score and can be calculated into the frailty index (FI). FI is a score from 0 to 1, in which 0 points are no deficits whereas the maximum of 1 point is the accumulation of all possible deficits [42]. A suggested cut-off for definition of frailty is above 0,25 [43].

A model describing frailty with both its possible reasons and its clinical presentation is the multi-layered model by Ferrucci et al. [6]. Here, frailty is stated as a construct of three overlying dimensions that are comparable to the layers of an onion. The superficial layer is the clinical presentation of a patient with the main features of multimorbidity and reduced physical and cognitive functioning presenting with slow walking speed, dependency, impaired memory and other geriatric syndromes. In addition, this layer is characteristically dynamic: Functional reserves, resilience and recovery are fluctuant and may improve, but often, frail patients are stuck in a downwards spiral to deteriorated health and impaired functional status [6].

The second, intermediate layer is called “area of biomarkers” and tries to provide possible pathophysiological mechanisms of frailty like reduced muscle mass and reduced physical activity, impaired homeostatic regulation mechanisms, inflammation and neurodegeneration. Without being clinically visible, those changes in physiology might be early manifestations of frailty, representing reduced organ reserves and lowered resilience of physical systems [6].

The core layer includes biomolecular changes, which are hypothetically the biological basis for both ageing and frailty: Oxidative stress, dysfunction of mitochondria and damaged DNA [44].

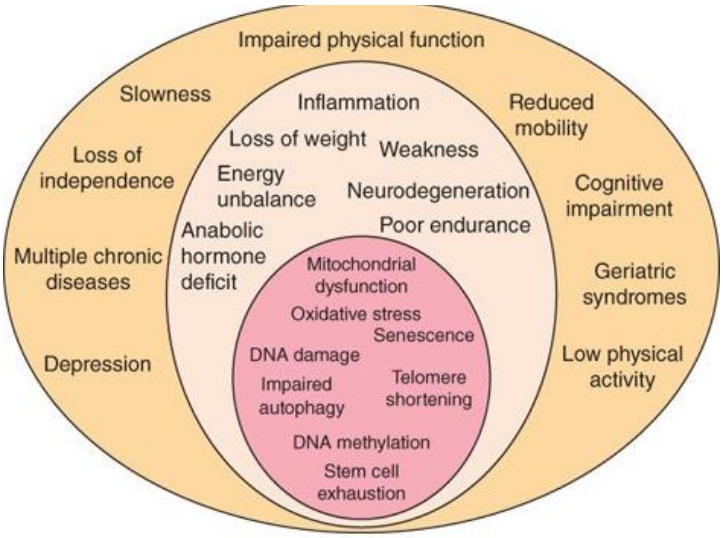

Fig. 1: The three dimensions of frailty according to Ferruci et al. [45]

According to Ferrucci, the frailty phenotype cannot be monocausal or based on a particular dysfunctional process; instead, it is rather the endpoint of various intertwined dysfunctions, disbalances and damages in the inner layers. Once relevant disbalances in different systems have occurred, the frailty phenotype becomes clinically apparent. The manifestations of frailty are furthermore dependent on the individual's preconditions like lifestyle and influences in life [6].

The lack of a clear definition of frailty – once used as geriatric syndrome and once as an independent condition - and therefore, also the lack of a standard instrument leads to varying estimations of its prevalence [46].

On the other hand, frailty research has to be translated into clinical practice in order to verify research questions in clinical studies. Therefore, time and expertise are required and can also be a practical limitation of broad CGA and frailty measurement [35]. For clinicians, the use of a frailty instrument is helpful in decision making when discussing medical interventions [38]. Due to the multidimensionality of frailty, the trend is moving to specific instruments for specific settings instead of developing a one-fits-all assessment [38].

The multidimensional approach to the definition of frailty and the acknowledgement of its complexity should be the basis of the routine assessment of frailty since many studies have reported multiple negative influences of frailty.

Studies showed that the higher a person's clinical frailty score, the lower his or her probability of survival [35,42,47].

Other associations between frailty and adverse outcomes are disability [39,48], impaired mobility [39], falls [49], hospitalisation [35,50], need of long-term care [35] and institutionalisation to nursing homes [51].

Outcomes regarding psychosocial manners are loneliness [52], depression [53], cognitive impairment [54] and in special interest of this work, worsened quality of life [55,56] and health-related QoL [57].

Knowledge about progression of frailty is still limited [58], but the good news is that frailty is not a fixed state but a dynamic construct, which can change over time, meaning that e.g. a prefrail person may become robust again [38].

Frailty illustrates the high variability of health states in older age much better than the collection of single diseases [59]. Therefore, frailty may be considered as a parameter reflecting the biological age of a patient [9] and as such might help improve decision making in public health more than the obsolete "chronological age" [9]. In clinical practice, frailty is used for holistic decision making about treatments and provides care based on a patient's individual needs [59].

2.1.4. Approaches on the assessment of frailty

Frailty as an approach of explaining vulnerability and decline in older age has gained increased regard. Its measurement seems to be another controversy with many different approaches. In this chapter, some approaches to its measurements are discussed. The first example is a very short assessment of the frailty-screening in emergency department, namely the clinical frailty scale (CFS). The interviewer assesses the patient's abilities about two weeks before hospitalisation according to the following scale:

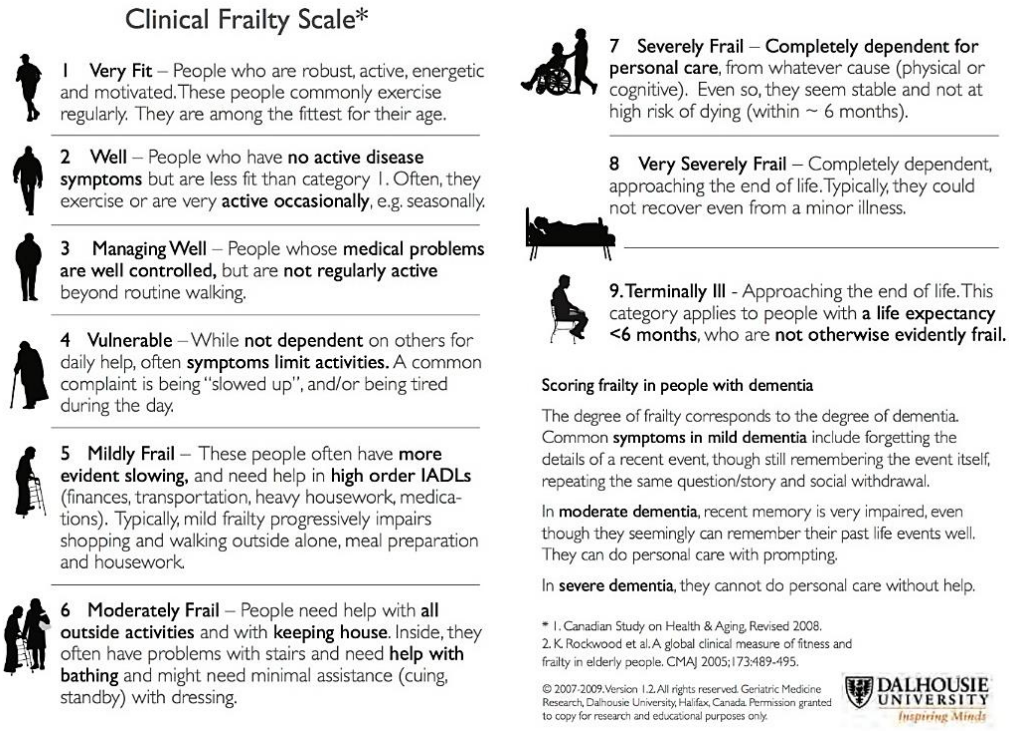

Fig. 2: The Clinical Frailty Scale [60,61]

Scoring 5 or higher indicates frailty in different severity scores [61]. Using the clinical frailty scores, outcomes like in-patient mortality, length of hospital stay as well as rehospitalisation can be predicted [62–65]. Being conducted in a very short time, the CFS can be effectively used in the emergency department.

Other approaches have been named previously when discussing Fried's frailty phenotype and Rockwood's frailty index. As a screening tool, both the clinical frailty scale or Fried's frailty phenotype are not feasible for capturing the underlying causes of frailty and therefore developing interventions against frailty [9]. In addition, they focus only on physical domains without recognising other factors lying beyond [9].

An approach to frailty trying to capture the multidimensionality and heterogeneity of frail patients is the Comprehensive Geriatric Assessment (CGA). It is not describing causes and risk factors like Ferrucci's onion model but is a detailed and overarching tool assessing the superficial frailty-layer of clinical presentation. Its concepts and tools are described in the following section.

No matter which tool is used, there is a broad consensus between European and U.S.societies that all individuals older than 70 years should be screened for frailty [66]. The clinical usage of CFS in emergency settings could be a practicable start of a broad implementation of frailty detection. Bringing frailty into clinical routine always needs the further step of translating the knowledge of frailty into targeted counteractions [9].

2.2 Comprehensive Geriatric Assessment

Addressing the complexity of geriatric patients, only a multidimensional tool can bundle all relevant dimensions and give an overview on the patient's conditions, like his resources and deficits. The most successful method for receiving such an essential overview is the Comprehensive Geriatric Assessment. It had its very beginnings in the 1930s, when Warren and colleagues developed first ideas for "care of chronic sick" [67]. Since those times, CGA became the gold standard for detection of frailty [35] and for the multidimensional assessment of frail inpatients [68]. It includes functional and emotional status, health, social resources and environmental conditions [4,7,69].

Most of the developed tools concur in the four main domains of physical health, psychological health, functionality and socioenvironmental status [70,71], and most reported assessments used in CGA-publications provide medical, psychological, social and functional information [68]. Components in detail are e.g. comorbidity, polypharmacy, mobility, activities of daily life, nutrition, emotional and mental status, social networks, living conditions, education and

financial resources [4,70,71]. To sum up, CGA provides a multidimensional insight and an estimation of a patient's participatory capacity in life [4].

The aim of CGA is, amongst capturing heterogeneity of population health [7], the assessment of a multidisciplinary profile [4]. Based on that, the development of holistic and patient-centered treatment strategies is possible [72]. Cornerstones of those treatments are the reduction of disability, improvement of independence and increasement of quality of life [72].

Studies on positive effects of CGA in different settings demonstrate several positive health outcomes like in survival [70,71], disability [71], cognitive function [4,71] and reduced rehospitalisation [4]. In comparison to routine medical care, Ellis et al. showed in a review article, that within one year of follow-up, older patients receiving CGA are more likely living at home and are less often admitted to long-term care homes, respectively [70]. Even patients in full health can benefit from CGA, not only the frail and multimorbid [72]. By capturing the phenotypic age, which may be substantially discrepant from chronological age, CGA identifies older persons at risk for the vicious cycle into functional decline [7].

2.2.1. The Multidimensional Prognostic Index (MPI)

The MPI is a comprehensive tool, developed by Pilotto and colleagues in order to extend CGA to a prognostic instrument for older inpatients [73]. It is based on eight different domains, which are assessed by validated instruments that are frequently used in clinical practice: Multimorbidity by Cumulative Illness Rating Scale (CIRS) [74], daily functionality bay Katz's Activities of Daily Living (ADL) [75] and Lawton's Instrumental Activities of Daily Living (IADL) [76], cognition by Short Portable Mental State Examination (SPMSQ) [77], nutrition by Mini Nutritional Assessment – Short form (MNA-SF) [78] and mobility and risk for pressure ulcers by Exton Smith Scale (ESS) [79]. The number of prescribed drugs as well as living conditions (alone, with relatives, in assistance) are assessed without a specific questionnaire [73]. Each questionnaire is divided into tripartite scores, which lead to a hierarchy of problems/functional deficits. In sum, information of 53 clinical items lead to calculation of an index, which gives information on the individual risk score for several adverse outcomes between 0 (no-risk) to 1 (higher-risk) [73]. The index can then furthermore be divided into three risk groups, which are concordant to frailty graduation: Low risk (MPI-1 0 – 0.33) / robust, intermediate- risk (MPI-2 0.34 – 0.66) /pre-frail and high risk (MPI-3 0.67 – 1)/ frail [73]. The graduation enables clinicians to identify risk groups for vitious cycle into functional decline and dependency rapidly.

Since its development, the MPI has been established as a comprehensive tool for the assessment of frailty and clinical prognosis [3].

In comparison with other frailty instruments, the MPI has the highest predictive accuracy for prediction of all-cause mortality after one month and one year in older inpatients [80].

It furthermore showed the highest sensitivity in detection of frailty and highest specificity for mortality, compared to screening instruments for frailty on patients admitted to hospital [81].
Measurement of frailty using the MPI is validated both in research and in clinical practice [82]. Compared to prognostic indices for older people, the MPI is a well calibrated tool with good discrimination regarding mortality [83]. In the past years, different versions of MPI have been validated, e.g. the Selfy-MPI for self-use of community-dwelling older people [84] or a Tele-MPI [85,86], developed and validated in times of Covid-19-lockdown as a phone-call assessment. Since MPI needs about 20 minutes for administration due to means of multidimensionality and comprehensiveness [81,87], a shorter MPI was developed, the BRIEF-MPI for a quicker approach to multidimensional frailty [88].

2.2.2. Clinical usage of MPI

The MPI as an established instrument for the assessment of frailty and clinical prognosis [3,43] has shown its effectiveness in several settings of in- and outpatient care:
In inpatients, it predicts hospital mortality, mortality one year after discharge and length of hospital stay [89–92]. Further outcomes are institutionalisation [93], rehospitalisation and the need of home care [84]. In a German observation, different associations to utilisation of resources of the German health care system like prolonged hospitalisation, grade of care and discharge to e.g. nursing homes were found [93].
Even during hospital stay, the MPI monitors sensitively the change of functionality and health [94] and is a useful tool also in non-geriatric settings to attend to patients with prolonged hospital stay [95]. In the emergency department, MPI seems to be related to patient's health-related quality of life [96].
In primary care, a study sample of 125 patients showed significant associations between higher MPI-scores and adverse outcomes as well as an average number of general practitioner consultations per year [97].
Regarding diseases, the prognosis of many common health problems is predicted by MPI, like pneumonia [98], Covid-19 [99] and respiratory failure [100], heart failure [101], advanced solid cancer [102], chronic kidney disease [80,103], diabetes mellitus [104], infectious complications [105] and acute bleeding complications in gastrointestinal tract [106] as well as oral health [107]. Furthermore, depressive disorders can be screened and monitored by MPI [108,109].
The MPI_AGE project, conducted between 2008 and 2013, had the aim to develop guidelines for clinical decision-making in older, multimorbid patients [92]. Many studies observed the risk-benefit ratio for several therapeutic interventions like transcatheter aortic valve implantation [110,111], surgery in colorectal cancer [112], percutaneous coronary intervention in acute myocardial infarction [113], renal replacement therapy in chronic kidney disease [114] and enteral tube feeding [115].

Further observations are on pharmacotherapy decisions like anticoagulation in atrial fibrillation [116], antidementia drugs in dementia [117], and secondary prevention using statins in coronary heart disease [118] and diabetes mellitus [119]. By conditioning clinical decisions on a Comprehensive Geriatric Assessment and the degree of multidimensional frailty, patient-centred and better decisions are warranted [120].

2.2.3. Geriatric resources

Despite functional, cognitive and social decline, subjective wellbeing seems to be quite stable in older age [121]. Personal resources as well as resilience and experience of life could be part of the explanation of this paradox of wellbeing [122]. Resources in general are means which help individuals managing daily tasks and dealing with adverse conditions [123,124]. Those means include physical and mental health, interests and capabilities, experiences in and attitudes to life as well as social webs and the economic standing [124].

Personal and extrapersonal resources in older age can be subsumed in the term “geriatric resources” (GR). Martin et al. state that the use of resources leads to positive adaptions in life like health promotion, prevention strategies and improvement of environment. In this manner, adverse effects and stressors can be attenuated and positive outcomes like quality of life and wellbeing are ameliorated [123].

Geriatric resources enfold all circumstances of living[125]: At first, activities and experiences like everyday activities and biographic experiences are considered as resources. Here, mnestic resources and competence-related resources can be subclassified. Furthermore, there are emotional resources like positive feeling and self-esteem. Motivational resources include orientation in action and self-efficacy and social resources are defined by social networks and positive environment [126] like good living conditions and economic resources. Furthermore, there are intellectual or cognitive resources as well as physical resources [127]. Religious or spiritual resources also seem to have important impact [128].

However, the systematic collection of GR in hospitalised patients is not established to routine. There are models of ageing postulating that optimization of resources and reduction of deficits may improve wellbeing [129].

Forstmeier et al. also state that activation of resources on the basis of resource assessment is an important factor in psychologic wellbeing in the elderly [126]. Social resources are investigated in detail due to their importance for health [130] and wellbeing [131] in older age. Social support takes effect by both emotional and instrumental support [131]. Contacts with friends or family lead to all sorts of activities and gives a feeling of security and familiarity [132], other GR like physical, emotional and motivational resources can hereby be maintained.

Furthermore, social resources positively influence coping [130], life satisfaction and optimism [133]. The experienced social support between older individuals >65 years is rather low.

In both sexes, only 25% experienced strong support [130]. A worsening factor for poor social support seems to be the educational level: social support is even worse in persons with lower educational levels [131].

In a longitudinal study, physical, intellectual, emotional and competence-related GR were significantly associated with a better prognosis and lower rates of rehospitalization [134]. The same results were shown for the relation between GR and GS. Having more GR than GS is a predictor for better outcomes, measured by a Comprehensive Geriatric Assessment [134].

2.2.4. Geriatric syndromes

By definition, a syndrome describes the accumulation of symptoms which can give a hint on the underlying disease, e.g. headache plus fever and meningism as a combination of typical symptoms of bacterial meningitis. Regarding geriatric syndromes (GS), the correlation of syndromes and underlying diseases is more difficult and in consequence the allocation of patients to specialized medical wards is hampered [37,135]. Geriatric syndromes are of multidimensional nature [37,134]. Their basis are several deficits and multifactorial conditions in many organ systems, that cannot be reduced to a specific disease pattern [135].

In turn, the multidimensionality of risk factors influences the cascade of clinical presentation of symptoms, diagnosis, course, patient's capacities, treatment need, response to therapy and outcome [37]. Meyer et al. state that GS result from a mixture of underlying multimorbidity, acute illness and age-related changes [134]. Accordingly, there is a high coincidence of multimorbidity and presence of GS [136].

The plurality of geriatric syndromes includes instability, immobility, falls, isolation, impoverishment, incontinence, inanition/malnutrition, swallowing disorders, polypharmacy, iatrogenic disease, chronic pain, cognitive or sensorial impairment, irritable colon, insomnia, delirium, electrolyte or fluid imbalance, irritability/depression and frailty [5,134,135,137–141]. In literature, frailty is allocated variably: for some authors, frailty is counted to GS [142], for others, frailty is rather a condition, amongst others, defined by the presence of GS [37].

The list of GS shows clearly the multidimensionality and complexity of geriatric medicine and the need of interaction of different medical disciplines.

Against the common perception that GS are normal or unpreventable result of ageing process [134], GS should be recognized routinely and early in diagnostic process in order to reducing disease burden and therefore reducing costs and preventing disability and hospitalization [143].

Several studies have shown significant associations between GS and negative outcomes, poor health outcomes in particular [135]. GS are furthermore associated with the patient's prognosis [134], quality of life [37,144]and disability [37].

Even in non-geriatric settings, all those GS can occur in older patients due to their multisided appearance. Studies showed significant interrelations between the Multidimensional Prognostic Index and the number of GS and GR [134]. The collection of GS could be a first step to a routine implementation of CGA in clinical practice and to therefore improve the patient's outcomes [71].

2.3 Quality of life (QoL)

Defining quality of life is a complex and discussable topic and differs whether considering its sociological, psychologic or health-related aspects. The crucial point in QoL definition and measurement is its nature of being a construct, which means, that the phenomenon is not objectively measurable and therefore only indicators or symptoms are providing information on the underlying issue [145].

The development of broader discussions and investigations on QoL, not only in medical contexts, began in the 1970s: Based on personal resources, 1974, Erikson et al. defined Quality of Life in an alleged objective manner: QoL is understood as the extent in which available resources are used to purposefully influence living circumstances [146]. Critics on this idea were appointed by advocates of a subjective QoL-concept: The perception of having control and freedom of action rather leads to improved QoL than resources themselves [147].

In 1995, about twenty years after the first mention of QoL as a new outcome factor, the World Health Organization (WHO) generated its own definition of QoL: The WHO defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [148].

As the WHO indicates, QoL must be seen as a multidimensional construct that has various interrelating subjective and objective components [149], is linked to wellbeing and functioning [150] and results of successful living and its ethical considerations [151]. In contrast to other concepts, QoL always presumes a judgement on values. The individual must ask himself: "What is it that makes my life valuable?" [147]. Someone who perceives his life as valuable and successful should therefore rate his QoL highly [151].

The QoL-dimensions include physical, emotional, mental, social aspects as well as everyday functioning [152]. On the other hand, all those dimensions are framed by other life-domains like welfare, societal resources and (post-)materialistic affluence [153].

Phrasing those definitions the other way round, QoL is a condition, in which a person can unfold his characteristics, live out his values and beliefs and therefore experiences his life as successful and reasonable [151]. Woopen et al. state that every asking for QoL is a more or less explicit indication for a commonly called "good life" [151].

Therefore, QoL is even more than wellbeing, since subjective wellbeing is only a psychologic construct without central involvement of ethic subjects, whereas QoL results of successful

living and its ethical considerations [151]. Other authors state, that QoL goes beyond wellbeing since it does not only include the affective and evaluative components of wellbeing but considers also broader components like physical, spiritual, social and emotional components [126].

Later on, a couple of assessments were developed and firstly established. As a pioneer discipline, oncology defined QoL as an important health outcome in their clinical studies, e.g., rating breast cancer therapies [152,154].

In research, QoL is often poorly defined. Fayers and Machin argue that often the authors are describing their very own theory of QoL and are letting prove this opinion by means of their questionnaires [154]. Consecutively, the implementation of QoL is driven by the assessment tool which was used [155]. Due to the operationalising definition of QoL, Costa et al. are concerning that investigators could measure whatever they want to. This idea is affirmed by a review article from Haraldstad et al. in 2019: Out of 163 studies, only 13% defined QoL and only 6% differentiated between overall QoL and its subdomain health related QoL (HRQoL) [156]. Though most studies provided at least QoL-domains and declared their selection-criteria for the used instruments, the authors concluded that there are immense opportunities for improvement regarding concepts and methods of QoL studies in health and medicine research [156]. In addition, different concepts of QoL lead to a lack of comparability [155].

Examining the plurality of measuring instruments for QoL, Fayers and Machin found a very precise comment: “Because there are so many potential dimensions, it is impractical to try to assess all these concepts simultaneously in one instrument” [154]. It is therefore important for research quality that investigators precisely define their conceptualisation of QoL and their decision making for the chosen assessment tool.

Regarding QoL-research in medical contexts, the term health-related quality of life is used frequently and will be discussed in a following chapter.

2.3.1. Quality of life in older age

In older age, multimorbidity, neurodegenerative diseases and need of care are significantly rising [131]. Nevertheless, many of the older individuals proof the paradox of wellbeing by rating high QoL despite decreasing objective resources [157]. Mental adaption processes seem to compensate physical and functional impairments [158,159] and perceived wellbeing loses its correlation to objective factors.

The ingredients for wellbeing vary for older people[28]: Besides participation, life satisfaction, mental and physical health as well as socioeconomic indicators seem to have an impact on QoL in older age [160]. Especially poor socioeconomic conditions lowered QoL as shown in different QoL ratings between eastern European and northern European countries [160].

Regarding environmental factors in general, Gobbens et al. found out that especially housing, residents and nuisance were the most influencing factors in QoL in adults aged 65 years and older [161].

In a more external manner, mobility seems to have an impact on QoL in older age as it provides social participation and independence [132].

Another study group focussed on psychologic factors like self-efficacy, hope and personality [162]. Overall, persons with higher rates of self-efficacy as well as persons who had a successful accommodation to changes in older age had higher wellbeing rates. Regarding the oldest age group, there was an outstanding difference to younger groups: The question of whether one can still realise personal goals in the remaining lifespan becomes increasingly important for self-rated wellbeing in the oldest old [162].

To sum up, internal factors like self-efficacy as well as external factors like functionality and social participation influence QoL in older age. By preservation of external resources and empowerment of internal factors QoL may be held up high.

2.3.2. CHAPO Model

The CHAPO Model tries to give a multidimensional model of QoL in very old age. Its theoretical background is based on Veenhoven's 4 Quliaties of Life model [163] and was expanded based on the results of "the Quality of life and well-being of the very old in North Rhine-Westphalia NRW80+ study". Here, 2000 community-dwellers older than 80 years were asked for their quality of life and its determinants [164,165]. The model subdivides personal and environmental factors on the one hand and one's life's results and chances on the other hand.

Regarding all dimensions of quality of life, a comprehensive view on this topic is possible.

Important issues in high age were social interactions and spirituality as well as protective and growth-orientated values [164]. In this model, the difference between QoL and wellbeing becomes clear, since wellbeing is only a small part of a person's life results and its appreciation.

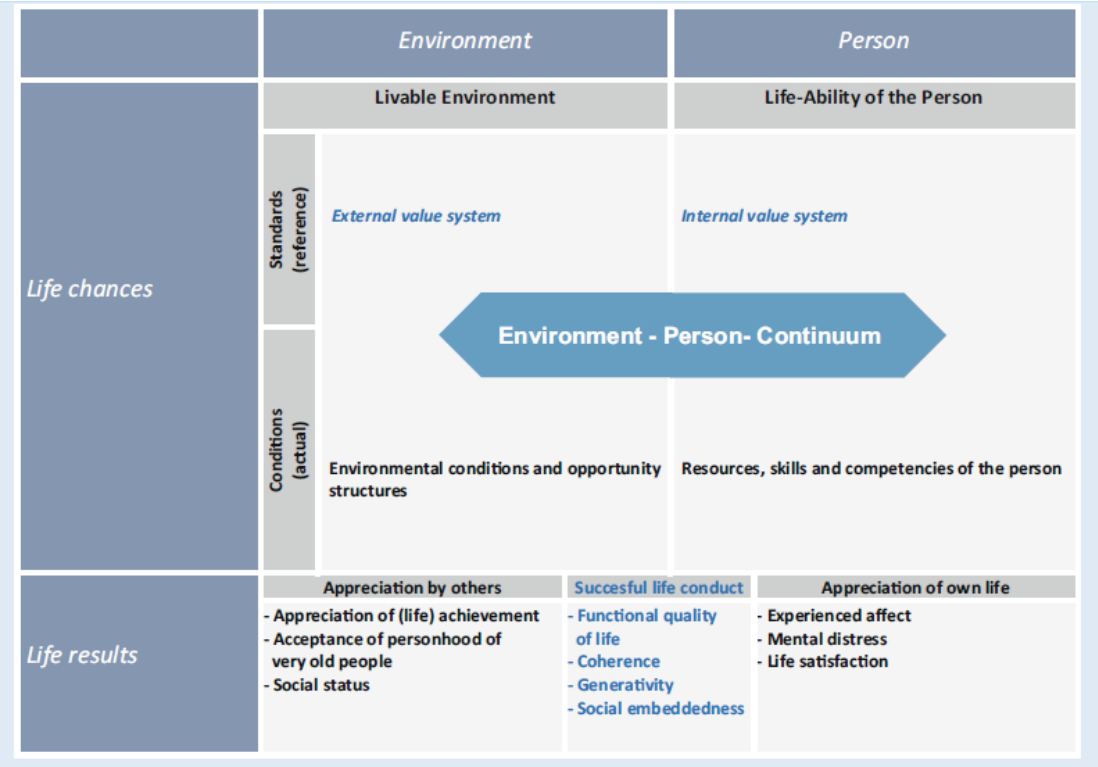

Fig. 3: The Chapo Model [165,166]

2.3.3. Measurement of quality of life

Due to its multidimensionality and inconsistent definition, measurement and research of quality of life are heterogenous. Measuring a construct, which is interpreted differently by every researcher, leads to as many definitions and conceptualisations [155,167]. There are both numeric and qualitative tools and their possible applications range from disease specific to economic issues. Researchers have to get deep into the numerous ranges of tools in order to find one that will fit best for their research question. The responsibility of the researcher is then to give a clear explanation of his QoL definition and his operationalisation [155]. Comparability between studies will remain challenging, but on the other hand, only the range of definitions and concepts can acknowledge and respect the multidimensionality and complexity of QoL.

Regarding comparability of questionnaires, a relevant problem might be the interpretation results and associations to other issues. What if there is a relevant discrepancy in QoL when using different questionnaires? [1]. Another problem might be in interpreting changes in QoL. What if one questionnaire proves the effectiveness of an intervention to improve QoL whereas another tool does not show significant impact? [155]. Researchers could fill this gap by using different tools at the same time and discussing potentially occurring different results. The limiting factor is time of the investigator and the attention span of their patients.

The WHO developed the WHOQOL-OLD to address important issues in older life like sensorial impairment, autonomy and participation [168].

2.3.4. Successful aging

When discussing QoL in older age, the thoughts of successful aging appear automatically. Hansen et al are defining successful aging as “autonomous, generative, active or productive behaviour by using respective educational, social, infrastructural, technical or economic resources” [164]. On the first sight, both definitions of QoL and successful aging seem to be quite similar or even consistent. On the other hand, someone who is living seclusively might not have successfully aged according to the afore stated definition even though he might rate his QoL high [151]. The main difference between QoL/wellbeing and successful aging is the ethic core of successful aging. It is seen as something desirable for its own sake without purposes beyond whereas QoL is rather a psychologic construct of wellbeing [151].

Definitions are frequently primed by a researcher’s question. The German Altenbericht 2001 therefore illustrates definitions of successful aging dependent on different key aspects: a medical definition: “Recovery and maintenance of health, capability and self-dependence”, a psychologic definition: “accommodation to challenges and deficiencies” and an economic definition: “social participation, financial resources and security” [124].

Regarding the heterogeneity of aged population, integrative definitions of successful aging could focus on autonomy and wellbeing [169]. Aging with dignity and independence are considered as core concepts of successful aging, as well [170]. Black et al yielded six topics, which should address this construct: “Meaningful involvement, aging in place, respect and inclusion, communication and information, transportation and mobility, and health and wellbeing” [170]. Those topics show the comprehensive view on older age’s issues. In their study, a great impact on aging independently were physical, mental, and social wellbeing as well as – as a basic requirement – staying healthy [170].

Comparable to these findings, Kim et al. examined the strength of association to the domains of successful aging: They identified prevention of disease/disability, high physical and cognitive function, activity, and psychological adaption as main influencing factors on successful aging [171]. In their study, the strongest association was psychological adaption in later life [171]. Having a high accommodation to changes in older life seems to have both a positive influence on QoL in older life as aforementioned, as well as on successful aging in general [162,171]. The core concept could be subsumed as person-environment fit with characteristics like experience of security, activity, continuity and meaning of life [127].

2.3.5. Health and self-rated health state

Trying to understand the tight interrelations between QoL and health and the later discussed health-related quality of life, the term “health” and especially “self-rated health state” need to be considered in detail.

Health, according to the WHO, is a state of complete wellbeing and not only the absence of illness [172]. The perception of this health state is captured by self-rated health state and is for example measured by the Euroquol-questionnaire, which captures self-rated health by a visual analogue scale between 0 and 100 points [173].

Subjective measurements often have a higher risk for response shift bias, meaning that differences in individual evaluation standards lead to varying value attribution [174].

Karimi et al investigated the principles on which the evaluation of self-rated health is based: Firstly, patients rated their health state in comparison to imagined or experienced ill health. Afterwards, the personal affection of health problems on individual interests and on the personal environment was rated.

Thirdly, participants estimated the consequences of their health state for non-health subjects like daily activities, independence, social relations, and enjoyment [175]. Moreover, the comparison to health-states of people of the same age are part of the evaluation [40]. These considerations may lead to differences between objective health state and self-rated health, particularly in older age [40].

The studies prove that there is a multidimensional view on perceived health state. Regarding older people, their concept of health seems to be quite stable even if the count of significant health problems rises. A possible cause could be that their standard of good health is lowered over time [176].

The importance of self-rated health is shown by different studies, which prove its prognostic significance: patients reporting worse subjective health than it was objectively assessed by a physician had increased mortality [177]. Other associations of self-rated health of older people are poor mental health, poor social support and chronic diseases [178] as well as sociodemographic characteristics, lifestyle and functional limitations [179].

A crucial point in health-state measurement is that measure of perceived health often is confounded with the measurement of function [180]. Brenowitz et al. conducted a longitudinal study in which only a little reduced self-rated health could predict decline in a person's functionality. But what is more remarkable, an inverse relation between poor physical functioning leading to alteration of self-rated health could not be observed [181].

As there are associations between self-rated health and functional status especially in older people, both terms should be assessed separately and with the knowledge of potential confounding. Some authors even recommend the development of function-neutral measures of self-rated health [180].

2.3.6. Health-related quality of life

Although many authors don't distinguish between both QoL and HRQoL [156], the term HRQoL should be used in health or medicine contexts in order to avoid ambiguity [154].

It is broadly accepted that the following aspects are key domains of the multidimensional HRQoL construct: physical and emotional health and social functioning [145,152,154,182,183]. Looking at the author's definitions in detail, there can be found additional aspects like cognitive functioning and existential issues [154], subjective perceptions of behaviour- and function-related aspects of wellbeing [182] or functioning in aspects of daily living [145].

Some researchers even don't use the term "health" in their definition of HRQoL and reduce HRQoL as a "subjective measure which is evaluable over time and having a focus on the qualitative dimension of functioning'' [184].

The following figure, developed by Vetter et al., tries to differ HRQol from QoL and health as the following:

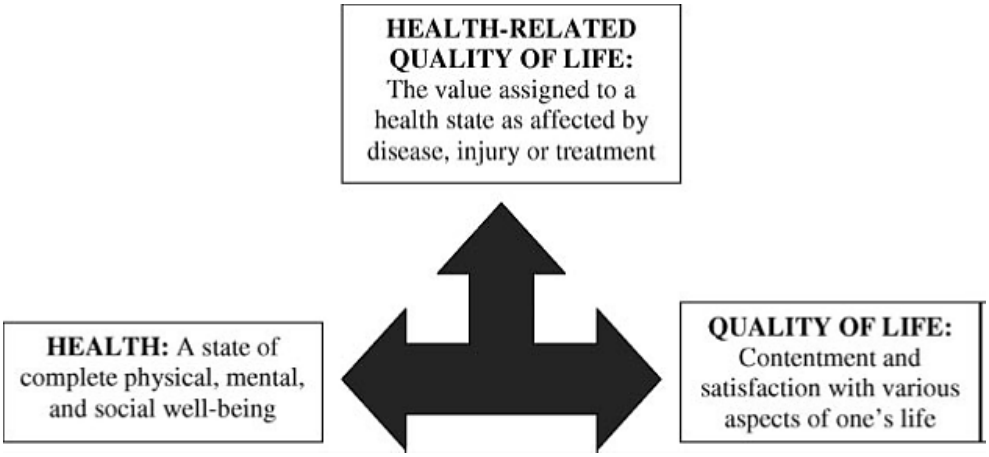

Fig. 4: "The interconnected relationship between a patient's state of health, quality of life, and health-related quality of life" according to Vetter et al.[185]

Here, the differentiation between the three subjects become clearer since the health component of HRQoL is underlined and differs the subject from overall QoL, which rather regards various aspects of life.

Years later, Bakas et al. were still complaining about the low consistency of HRQoL definitions and variable terms for concordant HRQoL concepts [186].

In their current opinion article, Karimi and Brazier criticised the lack of consistency and the lack of distinction between the terms health, QoL and HRQoL [187]: They identified and considered the suitability of four common HRQoL definitions, which are presented in the following:

In the first definition, HRQoL is based on the perceived wellbeing of health in physical, mental, social and functioning aspects [188]. The second discussed definition describes HRQoL as only the health aspects of QoL. HRQoL therefore excludes QoL-issues like economic and political circumstances [189]. However, both definitions seem to resemble the WHO definition of health as "a state of complete physical, mental and social wellbeing" [172].

Thirdly, HRQoL is described as the influences of health, illness and treatments on wellbeing [190]. In the author's opinion, there's no precise discrimination between QoL and HRQoL since

all domains of QoL can be directly or indirectly influenced by health in some way, even non-health topics like income or education. Furthermore, the impact of health on QoL can differ depending on whether a person is affected by e.g. physical or mental problems.

The fourth definition describes HRQoL with focus on the value a person assigns to his health state and the health effects on QoL and wellbeing [191]. The problem here is the frequent consideration of non-health factors whenever participants are valuing their health states [192]. Only if they qualify and quantify the health effects on QoL correctly, the HRQoL in this definition is distinct from QoL. The authors would name it then “health adjusted QoL” [187].

The demonstration of Karimi and Brazier summed up the aforementioned problem of defining HRQoL due to its overlap with health state and QoL.

The authors draw the conclusion of using HRQoL in two possible ways, namely either to indicate the value associated with health or to describe the way health influences QoL [187].

2.3.7. Measurement of HRQoL

For measurement of HRQoL, a variety of assessments have been developed. They evolve from combination of public health medicine and indicators concerning individual perceptions [190].

In clinical studies, psychometric questionnaires are used frequently [152,193]. Within the psychometric measurements, a basic differentiation can be made between generic and disease-specific questionnaires. Out of generic instruments, there are assessments that give an overview on profiles of HRQoL or those that provide an index calculation [152,193]. An established tool for HRQoL-profile questionnaire is the SF-36 [126]. It was developed for health status measurement, independent of age or specific disease [194]. The 36 items are subdivided into eight subscales including general and mental health, physical and emotional role, pain, vitality, and social functioning [194]. A physical component summary and mental component summary can be calculated and interpreted separately [194]. The SF-36 is a valuable tool for health restrictions in older age [126] and also appropriate for outcome measurement and comparison of treatment strategies as well as cost-utility measurement [145,185].

Another generic instrument for HRQoL-measurement is the EQ-5D [173,195]. Its five dimensions include mobility, self-care, usual activities, pain/discomfort and anxiety/depression [173]. The EQ-5D is particularly suitable for benefit-analysis and economic evaluations [167,193]. Due to its provision of an HRQoL-index, it can be used for economic evaluation like Quality Adjusted Life Years (QALY) estimation [196]. The index has a range between 0 (death) and 1 (perfect health) and is calculated on preference analyses of specific countries or regions. In Germany, e.g. the value set of Ludwig et al [197] is used, which has an emphasis on the mental domain of HRQoL. Preference weights of HRQoL-domains are included neither in the SF-36 nor in EQ-5D.

Disease-specific instruments focus on single diseases for example heart-failure or common states or symptoms like pain or dyspnoea. Other instruments include specific subpopulations like children or older patients [167].

Since there is no “gold-standard” for HRQoL-measurement, the use of generic or disease-specific instrument depends on the researcher’s question and study design.

Besides broad conceptualisations of HRQoL, also the plethora of measurement tools lead to comprehensive acquisition of knowledge in this field but makes general evidence and comparability even more complicated also due to the lacking differentiation to QoL.

2.3.8. What is known about HRQoL in research?

Due to its multidimensional character, the associations of HRQoL are broadly spread. Since there are numerous studies on several conditions in diverse age groups, this chapter aims to focus on associations which have impact on the underlying study group – older, frail patients.

Primary, frailty itself substantially influences HRQoL. Kojima et al as well as Crocker et al proved a consistent inverse association between frailty and QoL in a systematic review and meta-analysis, regarding cohorts of community-dwelling older people [56,198]. In frail people, QoL is lower compared to prefrail people and QoL declines over time [55].

Another important influencing factor on HRQoL, measured by SF-36, is disability. Both physical and mental scales decreased in general elder population even after adjustment for sociodemographic and social support and the presence of diseases [199]. Physical functioning plays even “an extremely important role” in QoL of older populations, according to Rizzoli et al who reviewed studies regarding frailty, sarcopenia and QoL [184].

Having lower mobility, impaired independency in self-care, reduced activity or pain are also associated with low HRQoL [200] as well as sarcopenia itself [201].

Despite QoL seems to be lowered even if the burden of diseases is statistically excluded, multimorbidity has also a proven negative impact on QoL [202]. Physical HRQoL decreases with rising count of diseases, especially dysfunctions in musculoskeletal system and peripheral artery disease and vascular diseases led to severe losses of HRQoL in older persons [203]. Mental domains of HRQoL were affected less by multimorbidity [203]. Other diseases like coronary problems, stroke, and diabetes mellitus as well as extreme body mass index (very high and very low) impaired perceived health state [204].

A meta-analysis, including more than one million participants confirms the strong interrelation between multimorbidity and poor QoL in different QoL scales. The analysis also found that each added condition deteriorates HRQoL even more [205].

Beside physical factors, also mental factors influence HRQoL like individual characteristics and socioeconomic issues [150].

Reduced self-responsibility and dysfunctional dependency led to impaired QoL over time [206]. Decreased ego integrity therefore was associated with Euroquol-domains like “depression”, “usual activities” and “discomfort” [122].

Typical geriatric syndromes like incontinence, chronic pain, sarcopenia, depression, isolation and poverty are associated with low HRQoL [207–209] whereas geriatric resources like social support, financial resources and behavioral factors are associated with improved HRQoL [210]. Other improving factors on QoL are coping-strategies and resilience [150].

Regarding severe outcomes, Otero-Rodriguez et al showed that decline of HRQoL is a predictor for mortality in older age [211]. Other studies proved the association between all-cause mortality and HRQoL in initially healthy people [212].

Regarding the plurality of influencing factors and outcomes, (HR)QoL cannot be ignored in study-design amongst older people.

2.4 Presentation of the underlying problem

In the last decades, both the assessment of frailty using a Comprehensive Geriatric Assessment as well as research on quality of life have gained rising attention. Even though associations between geriatric conditions and quality of life intuitively seem to be obvious, there is a lack of structured investigations on potential interrelations [213].

Expecting an immensely rising number of geriatric patients, geriatric medicine has to shift its focus from survival and elongation of lifespan towards quality of life and extended healthspan [2,214].

This thesis aims to give a structured view on HRQoL of older patients during hospitalisation on an internal ward. Moreover, the associations between HRQoL and geriatric syndromes and resources as well as the MPI should be described. By gaining knowledge about GR and GS which might have special impact on HRQoL, targeted treatment strategies could be developed in order to reduce the burden of negative geriatric conditions and therefore improve HRQoL.

The second aim is to discuss current approaches on frailty interventions, treatment of GS and promotion of GR.

The thesis is based on the original publication “the prognostic fingerprint of quality of life in older inpatients”. Methods and results of this study are shown below, the publication is cited in chapter 8 “pre-publication of results”.

3. Material and Methods

The study took place in department for internal medicine II of the University hospital of Cologne. Here, the medical focus is on nephrology, diabetology, rheumatology and internal medicine in general. The ward has a capacity of 34 patients. There is a high heterogeneity in the patient population, from young persons with isolated glomerulonephritis to older multimorbid patients under haemodialysis having acute infections or cardiovascular problems. From November 2018 to July 2019, patients aged 65 years or older were screened. In this period, 239 older multimorbid patients were admitted due to acute disease or relapse of chronic conditions. All of them underwent high-performance medicine like innovative and highly specialized clinical approaches.

Patients were included if they hit the inclusion criteria as follows: having 65 years or older, suffering from two or more chronic diseases with need of long-term treatment and being recruited and having signed the informed consent within the second and fourth day after admission.

Out of the screened population, 74 patients could not be included. Main reasons were poor knowledge of German language or speech disorders, as well as a delayed screening point outside of the given time window. Other patients weren't able to answer the questionnaire due to impaired health status.

After signing for informed consent, the Comprehensive Geriatric Assessment using the Multidimensional Prognostic Index was performed. In addition, the patient was asked for falls and hospitalizations in the past year and for his grade of care. With help of the doctor's report, basic data like age, source of referral, length of hospital stay, and the medical history were captured. In addition, medical treatment and medical imaging were recorded.

The MPI was performed, and its value has been calculated as explained in the introduction-chapter. After conducting the MPI, Geriatric Syndromes and Geriatric Resources were collected. Some of them doubled with already collected information like incontinence, instability, and polypharmacy, some of them, for example mnestic or motivational resources had to be asked for.

Quality of life was collected in two ways. First with a numeric rating scale in the four HRQoL-defining categories of physical health, mental health, everyday life, and social environment. Patients could score from one to ten points dependent on their subjective satisfaction with each category. A higher number indicated a higher QoL. Later, both the subdomains and HRQoL on average (using the mean value of the four categories) were calculated. Secondly, the European quality of life-5-dimensions, EQ-5D-5L, was used as above explained. Using both instruments, the rating scale could be compared with the established and validated measurement tool EQ5D.

At the time of discharge, the MPI was collected for a second time in order to evaluate changes e.g. in C.I.R.S- questionnaire or in the Activities of Daily Living. Moreover, the discharge allocation and medication were noted.

After three, six and twelve months, we conducted telephone calls. The follow-up included data of survival, rehospitalization, medication, and health-related quality of life. Patients who could not be reached by phone calls more than three times on different days and daytimes were stated lost to follow-up. In the underlying study group, 23% percent was lost to follow-up on any time.

Statistical analyses were performed with SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA, Version 25.0). A statistical level of significance was assumed at 0.05 for two-sided probabilities. Many quantitative variables were not normally distributed. Therefore, nonparametric analyses were used: Fisher's exact test was chosen for categorial variables, for analyse of metric variables, Kruskal-Wallis or Mann-Whitney-U-test were used. Afterwards, correlations of follow-up data were described by Spearman's Rho coefficient. Linear regression analyses on HRQoL and EQ5D were performed including all GR and GS and number of GR/GS respectively. The influence of GR and GS was analysed by stepwise backward selection. Furthermore, the regression analyses were adjusted for age, gender and MPI group.

4. Results

Demographic data and clinical characteristics of the study population are displayed in table 1[215]. The study group was characterized by a mean age of 75.9 years (SD 6.45 years) and a median MPI of 0.44. Half of the patients were in the moderate MPI risk group, 30% in ow risk and 20% in severe risk. About 60% of the study population were male and the median length of stay was 10 days (IQR 5.5-19 days).

Table 1: Study population

	Total	*HRQoL on average*			*p value**
	n=165	*0-3.3 points n=11(6%)*	*3.4-6.6 points n=74 (44.8%)*	*6.7-10 points n=80 (48.5%)*	
Gender male, n (%)	97 (58.8)	6 (54.5)	41 (55.4)	50 (62.5)	0.640
Age, mean (SD)	75.89 (6.45)	74.36 (5.52)	76.23 (7.05)	75.79 (6.01)	0.622

Living alone, n (%)	50 (30.3)	2 (18.2)	25 (33.8)	23 (28.8)	0.593
Source of referral: new admission, n (%)	65 (39.4)	4 (36.4)	27 (36.5)	34 (42.5)	0.770
Length of hospital stay, median (IQR)	10 (5.5-19)	8 (4-15)	12.5 (7-20.25)	9 (5-18)	0.256
Grade of Care ≥1, n (%)	71 (43.56)	4 (36.36)	37 (51.39)	30 (37.5)	0.198
Period of education, median (IQR)	11 (10.5-13.5)	12 (10-15)	11 (11-14)	11.5 (10-13)	0.939
BMI, median (IQR)	25.9 (22.7-30.21)	26.03 (21.9-29.1)	26.15 (22.8-30.65)	25.25 (22.53-30.21)	0.949
MPI, median (IQR)	0.44 (0.31-0.63)	0.5 (0.44-0.63)	0.5 (0.38-0.59)	0.38 (0.25-0.56)	<0.001
Number GR, median (IQR)	8 (7-9)	7 (5.25-7.75)	8 (7-9)	9 (7-10)	<0.001
Number GS, median (IQR)	6 (4-7)	8 (6-9)	7 (5-8)	5 (3-6)	<0.001
More GR than GS, n (%)	156 (94.5)	8 (72.7)	69 (93.2)	79 (98.8)	0.001
EQ-5D-index, median (IQR)	0.668 (0.392-0.861)	0.201 (0.028-0.475)	0.527 (0.295-0.761)	0.832 (0.571-0.960)	<0.001
**Kruskal Wallis Test for metric, Fisher`s exact test for nominal variables* *Significance level <0,05*					

Regarding demographic and economic factors, no significant association could be found between HRQoL on average and age (p= 0.914), gender (p= 0.381), and grade of care (p= 0.140). Neither source of referral (p= 0.879) nor length of hospital stay (p= 0.134) were significantly associated with HRQoL.

Between HRQoL and geriatric conditions, significant associations were found in linear regression models between HRQoL and MPI (p<0,001) as well as between HRQoL and number of GR and GS (p<0,001).
Both assessment tools for HRQoL, numeric rating scale and EQ-5D index, were significantly correlated with each other (rs= 0.560, *p*< 0.001).

The regression analysis for HRQoL found some specific GR and GS having significant regression coefficients: Immobility, chronic pain, depression, insomnia, fluid problems, swallowing disorders and motivational and emotional resources. Those subanalyses of GS and GR are shown in table 2 [215].

Table 2: P-values: comparison of HRQoL by GS and GR					
	HRQoL on average	QoL phyiscal	QoL mental	QoL everyday life	QoL social environment
Geriatric Syndromes (frequency in %)					
Incontinence (34.5)	0.026*	0.003**	0.052*	0.372	0.100
Instability (79.4)	<0.001**	<0.001**	0.007**	0.008**	0.022*
Immobility (41.8)	<0.001**	<0.001**	<0.001**	0.383	0.016*
Cognitive impairment (4.3)	0.055	0.041*	0.387	0.134	0.264
Inanition (7.9)	0.061	0.836	0.035*	0.171	0.010*
Chronic pain (47.3)	0.007**	0.005**	0.022*	0.054*	0.238
Polypharmacy >8 (57.6)	0.038*	0.104	0.491	0.116	0.412
Depression/irritability (17.6)	<0.001**	<0.001**	<0.001**	0.486	0.185
Sensorial impairment (64.8)	0.101	0.065	0.260	0.452	0.365
Insomnia (57.0)	0.021*	0.051*	0.136	0.050*	0.321
Irritable colon (49.7)	0.319	0.069	0.542	0.107	0.557
Iatrogenic disease (7.9)	0.513	0.099	0.669	0.927	0.913
Incoherence/delirium (6.1)	0.204	0.032*	0.045*	0.550	0.813
Impoverishment (8.5)	0.418	0.561	0.330	0.913	0.790

Social isolation (10.9)	0.001**	0.332	0.004**	0.019*	<0.001**
Fluid/electrolyte imbalance (44.2)	0.003**	0.019*	0.204	0.039*	0.103
Swallowing disorder (18.2)	<0.001**	<0.001**	0.034*	0.036*	0.057*
Geriatric Resources (frequency in %)					
Physical (76.8)	0.004**	<0.001**	0.083	0.162	0.130
Living conditions (74.4)	0.865	0.032*	0.717	0.738	0.752
Social (79.9)	0.001**	0.372	0.012*	0.017	<0.001**
Financial (79.9)	0.370	0.208	0.861	0.729	0.789
Spiritual (66.5)	0.036*	0.355	0.011*	0.263	0.092
Motivational (93.9)	0.002**	0.002**	0.060	0.041*	0.019*
Emotional (92.1)	0.002**	0.044*	0.002**	0.058*	0.037*
Mnestic (97.6)	0.251	0.525	0.951	0.077	0.305
Competence-related (70.7)	<0.001**	0.003**	0.177	<0.001**	0.001**
Intellectual (65.2)	0.399	0.431	0.671	0.846	0.281
Mann-whitney-U-test ** significant at 5% level* *** significant at 1% level*					

In further linear regression models, HRQoL was strongly associated with immobility (p= 0.001), chronic pain p= 0.009), irritability/depression (p= 0.003), insomnia (p= 0.035), fluid problems (p= 0.005), swallowing disorder (p= 0.001), motivational (p= 0.035) and emotional resources (p= 0.009) (R= 0.631, p< 0.001).

Regarding the follow-up results, 126 patients could be included in these analyses, 39 patients were lost to follow up. After 12 months, there were 52 deaths. Both MPI, number of GR/GS, HRQoL and EQ-5D index were significantly correlated with survival time (p< 0.05). Furthermore, HRQoL and MPI were significantly correlated with rehospitalisations (p= 0.010 and p= 0.039, respectively).

Table 3 shows further correlations between geriatric conditions, HRQoL and survival at follow-up timepoints.

Table 3: Spearman-correlation coefficients of inhospital CGA and Follow-up-HRQoL/survival days					
	6months Follow-Up		*12 months Follow-Up*		
	HRQoL (n=85)	*EQ-5D-index (n=85)*	*HRQoL (n=68)*	*EQ-5D-index (n=69)*	*Survival days (n=126)*
MPI	r=-0.208 p=0.056	r=-0.334 p=0.002	r=-0.213 p=0.081	r=-0.370 p=0.002	r=-0.470 p<0.001
Number GS	r=-0.405 p=<0.001	r=-0.417 p<0.001	r=-0,427 p<0.001	r=-0.471 p<0.001	r=-0.281 p=0.001
Number GR	r=0.246 p=0.023	r=0.245 p=0.024	r=0.363 p=0.002	r=0.462 p<0.001	r=0.259 p=0.002
HRQoL	r=0.528 p<0.001	r=0.382 p<0.001	r=0.434 p<0.001	r=0.356 p=0.003	r=0.224 p=0.008
EQ-5D-index	r=0.467 p<0.001	r=0.576 p<0.001	r=0.333 p=0.009	r=0.454 p<0.001	r=0.404 p<0.001

4.1 Previously undisclosed results

The study group and its main characteristics were already described above and published in the original paper by Heeß et al [215].

Further analyses were made for disease-severities according to the CIRS-questionnaire and its associations to HRQoL. The following table shows shows p-values for comparison of HRQoL variables between disease-severity-groups (from “0” no disease to “4” extreme severe disease) and HRQoL subgroups as well as HRQoL on average, additionally described by EQ5D-index:

Table 4: Comparison of HRQoL by disease severity groups, measured by CIRS (p-values)						
	HRQoL physical	HRQoL mental	HRQoL everyday life	HRQoL social environ-ment	HRQoL on average	EQ5D-Index
Cardiac (heart only)	0,603	0,441	0,768	0,379	0,242	0,26
Hypertension (rating is based on severity)	0,819	0,328	0,138	0,037*	0,273	0,227
Vascular (arteries, veins, lymphatics)	0,299	0,120	0,385	0,119	0,113	0,201
Respiratory (lungs, bronchi, trachea)	0,036*	0,086	0,229	0,530	0,069	0,808
EENT (eye, ear, nose, throat, larynx)	0,156	0,094	0,795	0,792	0,230	0,129

Upper GI (esophagus, stomach, duodenum, biliary and pancreatic trees)	0,230	0,880	0,777	0,683	0,788	0,799
Lower GI (intestines, hernias)	0,639	0,480	0,939	0,726	0,667	0,337
Hepatic (liver only)	0,035*	0,595	0,210	0,371	0,096	0,710
Renal (kidneys only)	0,162	0,628	0,768	0,657	0,471	0,548
Other GU (ureters, bladder, urethra, prostate, genitals)	0,070	0,154	0,459	0,390	0,070	0,130
Musculo-skeletal-integumentary (muscles, bone, skin)	<0,001*	0,034*	0,021*	0,112	<0,001*	0,232
Neurological (brain, spinal cord, nerves)	0,198	0,328	0,399	0,125	0,083	0,742
Endocrine-metabolic (including diabetes, hyperlipidemia, infections, toxicity)	0,956	0,710	0,730	0,129	0,675	0,382
Psychiatric (dementia, depression, anxiety, agitation, psychosis)	0,330	0,017*	0,141	0,020*	0,016*	0,346
Kruskal-Wallis test ** significant at 5% level*						

In this table, only few significant associations between organ systems and HRQoL were found. Interestingly, the numeric rating scale and EQ5-5D differed in some ratings. There were no significant associations between the EQ-5D index and CIRS-subgroups.

Regarding HRQoL on average, only musculo-skeletal- and psychiatric diseases have a significant association in this study group ($p<0,001$ and $p=0,016$). Both disease-groups showed also significant results when regarding subgroups of HRQoL. Musculo-skeletal diseases seem to be linked with physical QoL ($p<0,001$), mental QoL ($p=0,034$) and QoL of everyday life ($p=0,021$) and psychiatric diseases are associated with mental QoL ($p=0,017$) and QoL of social environment ($p=0,020$). Except respiratory diseases, hepatic diseases and hypertension, which were associated with single subgroups of HRQoL, no disease group showed significant results.

Combining clinically relevant respiratory and musculoskeletal diseases (CIRS-score >=2), concomitance of both disease groups was significantly associated with HRQoL on average (p=0.004) and EQ5D-Index (p=0.008). Associations with physical and mental QoL (p<0.001 each) persisted (Mann-Whitney-U-test).

A further analysis was carried out on HRQoL and number of GR/GS. Initial regression analyses on this topic were published in the attached paper.
Linear regression models for HRQoL on average were now repeated in a secondary analysis, this time adjusting for MPI-groups, trying to give a more detailed look into the associations of quality of life independently of frailty. In the final regression model, number of GS and GR each stayed significant after adjusting for age, gender, and MPI-group (R^2=0.320). Using the same independent variables in a linear regression on EQ5D-Index, number of GR slightly missed the stated significance level of 0,05 (p=0.052) whereas number of GS stayed significant (p<0,001) after adjusting for age, gender and MPI-group (R^2=0,569).

5. Discussion

5.1 Key findings and limitations of the study

The MPI_InGAH III study could be conducted as described in the study protocol without subsequent changes or encountered problems. A large study population of 165 patients could be enrolled in the period of ten months, which is nearly 70% of all screened patients.
The first key finding was the strong association between health-related quality of life and geriatric syndromes and resources. To our knowledge, this is the first study showing these associations. We found these associations not only for the absolute count of GR and GS. On addition, a profile of GR and GS which seemed to have the most impact on HRQoL could be identified.
Recent studies showed associations between the MPI and HRQoL in the emergency department of the university hospital of cologne [216] and between MPI and good QoL expectancy over a period of ten years [213]. In our study, we could affirm these findings by showing significant correlation between HRQoL and MPI-score.

By adjustment for MPI-groups in our linear regression model of HRQoL on average, we could prove that HRQoL is associated with GR and GS independently of frailty.

Thus, the complex interrelation between HRQoL and diverse geriatric conditions, represented by GR and GS, could be more outlined.

We can take this knowledge as a cornerstone for further research on these interrelations. Both, single GS and GR have to be analysed as well as clusters of GR and GS in order to find further relevant interactions and potentiation factors [217]. The aim should be to define red flags of e.g. GS-combinations with the most impact on HRQoL or to find GR which are worth being systematically supported in order to improve QoL.
In a second step, those GS and GR could become contact factors for targeted interventions and standardised treatment strategies.
A limitation of GR and GS is its dependency of the investigator since the collection is not standardized yet. As well the investigation might differ since varying GR and GS are included, and the interpretation of singe GR and GS might differ, e.g. whether one can have contrary syndromes and resources at the same time, e.g. immobility and physical resources. Similarly to definitions of QoL and frailty, investigators should discuss their definition and approach in the introduction section to warrant transparency.

In this study, a validated tool – the EQ5D 5L- was used as well as a numeric rating scale. Both tools showed strong correlation with each other (Spearman's $r= 0.560$, $p< 0.001$). Also, the results regarding MPI, GR and GS were similar. A noticeable difference between both tools is the similarity of EQ5D and the MPI. Both tools include activities of daily living, instrumental activities of daily living and physical conditions. The EQ5D differs from MPI by asking for fear or depression symptoms as well as for pain or discomfort. However, the numeric rating scale hat its focus on physical and mental health as well as on social interactions and activities of daily living and may therefore give a broader look on HRQoL without so much focus on functioning.

Another key finding was the prognostic value of HRQoL regarding survival time after discharge. Multiple studies described a prognostic significance for QoL [211,212,218]. In our study, both, the numeric rating scale as well as the EQ-5D index were significantly correlated with survival days after twelve months of follow-up. The correlation of survival time was also confirmed for the MPI and number of GR and GS. Regarding the Spearman-correlation coefficient, the MPI and EQ-5D had the highest values.
Monitoring HRQoL over time, there were no statistically significant changes after six and twelve months. HRQoL during hospital stay correlated significantly with its values at the follow-up timepoints, showing consistent and stable HRQoL. It remains unclear whether HRQoL is worsened due to hospital admission and stays lowered afterwards or if HRQoL stays stable despite hospitalisation. Longitudinal observation studies performed at a general practitioner or in a nursing home could help answering this question.

Moreover, multimorbidity using the CIRS-questionnaire and HRQoL were analysed.
Previous studies described multimorbidity as a risk factor for worsened QoL [205], which we could not affirm that clearly in our study (cf. Table 4). This might have several reasons. First, we used the "cumulative illness rating scale – CIRS", which does not collect single diagnoses but combines them into organ-groups like for example upper gastrointestinal tract or respiratory system. Diseases in this groups become relevant for the CIRS-score, if they have to be treated at the moment like, for example, by antihypertensive drugs regarding arterial hypertension. In that way, some diagnoses have no impact here, because they don't contribute to the CIRS-score [74]. Since we did not focus on common diseases but on restrictions in organ groups, the different result of our study could be explained.
Both single organ groups as well as the count of CIRS-score missed significance level for association to HRQoL. The only significant association could be shown for musculoskeletal diseases (P<0,001 for HRQoL on average), which might be biased, since musculoskeletal diseases like hip-fractures or rheumatoid diseases are graduated by their impact on functionality and limitation of mobility [219]. Maybe we measured the association of reduced functional status on HRQoL instead of the impact of an actual disease in the musculoskeletal system.
Another reason could be that the study group included predominantly multimorbid patients with nephrolocigal and cardiovascular diseases, many of them in need of dialysis.
There was no control group with non-multimorbid patients, so we could only compare different clusters of multimorbidity. In the context of high-performance medicine of a university hospital, where special diseases are treated individually, the impact of those particular diseases might lose its significancy in the cluster of multiple chronic conditions.
Regarding quality of life, the treatment of a single disease probably does not have direct benefits for our patients, also shown by the fact, that HRQoL stays stable after discharge, even though acute diseases were treated adequately during the hospital stay.

Internal medicine measures its success by organ function and inflammation parameters, e.g. when treating a pneumonia. Our results underline the importance, that all geriatric patients hospitalized in internal medicine should be screened for geriatric needs and in consequence be treated with a geriatric team. Otherwise, we cannot adequately face the crucial factors which lead to worse outcomes and decline of quality of life. Deducting treatment strategies, our study underlines the importance of the consequent use of a CGA or recording of GR and GS, respectively.
Studies showed that outcomes of geriatric patients improve significantly when using a CGA [70]. A recent study showed that establishing routine measurements of CGA on an internal ward could also shorten the length of hospital stay [95].

Moreover, patient- reported outcomes such as HRQoL or wellbeing need to be reported more often, since there is still a lack of evidence to date [68].

The limitations of our study were the small patient cohort, especially regarding the follow-up results. Given that about one third of the study group (52 of 165) died in the period between inclusion to 12 months after discharge, the collected follow-up data were naturally decimated. To have a more validated look on such data, bigger cohorts are needed.

A strength of our study cohort was the very detailed look on each patient. Due to the CGA, we gained a multidimensional view with lots of personal information. Especially the different approaches to frailty, using the MPI and geriatric syndromes and resources brings the benefit of validation and comparability. Moreover, the use of two questionnaires for HRQoL helps describing this complex construct more in detail.
In further studies, more patient-reported outcomes should be included in order to find out more about subjective and personal outcomes like QoL, wellbeing and life satisfaction.

5.2 Turnaround to a resource orientated treatment

Regarding geriatric resources, their significance for older patient's outcomes like prognosis, health, and especially quality of life, is still neglected [134,145]. Health systems are based on deficits, historically grown on the fact that nearly all diseases ground in reduced organ functions. They focus is on symptoms, geriatric syndromes, and physical decline. This strategy may have worked well for many hundred years in which younger populations suffered from infectious diseases. But in nowadays, geriatric populations are flooding hospitals, presenting plenty of symptoms and organ dysfunctions, which have become chronic and are not curable anymore [2].
For example, incontinence is a geriatric syndrome which will rather persist despite best medical care due to anatomic or neurologic deficits. In consequence, treatment strategies of older people have to focus on coping factors balancing all those persisting syndromes and diseases. Finding a way to systematically address coping factors, the concept of geriatric resources could be a first step to a resource and competence orientated diagnostic and treatment of geriatric population.
As stated in the introduction section, concepts like successful ageing and quality of life are not defined by only the absence of negative factors but on positive parameters and person's resources [148]. In consequence, also the geriatric assessment must include personal resources and a patient's perception of health to get a comprehensive view on a patient's situation.

Systematic collection of GR is needed to understand GR's associations to clinical outcomes in large cohorts and different settings.
In our studies, we included ten geriatric resources. Considering further studies, Forstmeier et al recommend implementation of even more resources like coherence, adaption to deficits, self-efficacy and self-regulation [126].
In adaption to the "ILSE-model", developed of results of the "Interdisziplinäre Längsschnittstudie des Erwachsenenalters", as well intrapersonal and extrapersonal resources should be included, with embrace of psychologically relevant resources in older age including cognitive, physical, and social resources, behavioural resources which interfere with health and wellbeing as well as environmental and community context factors [127].

Resource models assume that wellbeing and QoL can be increased by promotion of resources, equation of deficits and adaption of person-environment continuum [129]. In this conceptualisation, resources are stated as balancing factors which enable older people to maintain life satisfaction and wellbeing despite of age-related decline.
Van Ingen described a reduced mental burden due to loss of functionality and autonomy by having social support [220]. Religious or spiritual resources can help having higher life satisfaction and wellbeing and additionally help standing through challenges in life, including finiteness and death [128]. Further studies are urgently needed to describe patterns of geriatric resources and the mechanisms of specific impact on wellbeing and quality of life.

5.2.1. Approaches to improving quality of life

Due to its multidimensionality, QoL is hard to define and measure. Even more complicated or maybe impossible is to find one intervention, which will improve QoL in all our patients. Bullinger et al. therefore recommend the identification of QoL-problem-areas, which should be treated with tailored interventions [150,152].
To do so, individual value systems and circumstances have to be considered, and researchers also have to pay attention to age-related changes, for example in valuation of life. There are age-related differences in preferred values, namely when rating their life satisfaction, the younger-old underline the role of health factors whereas the oldest-old focus on social factors [159].
Available data regarding interventions to improve QoL could not show any clear benefit of health care interventions [221]. Rijckevorsel-Scheele et al. conducted a systematic review about health care interventions and their effect on QoL in elderly. The reported effects were inconsistent, especially in comparison to control groups, no significant differences were found in QoL-development [221]. The surveyed studies differed in many points, particularly in the modality of intervention (from testosterone gel to multidisciplinary treatment and exercise

program). However, regarding only multidisciplinary treatments five of nine studies could not find significant improvements of overall QoL in the intervention-group [221].

Improving health factors like physical capacity throughout an exercise program, in some studies, QoL and wellbeing as well as cognitive performance could be improved significantly [222,223]. Interestingly, both frail and robust patients drew a benefit from such interventions [222].

Also, the impact of psychologic interventions on QoL such as the effect of meditation were examined. Weber et al. showed in a metanalysis that mind-body interventions could successfully improve QoL and reduce depressive symptoms [224]. Furthermore, mindfulness training could improve QoL and depression in a smaller study regarding nursing home residents [225]. A review article by Sutipan et al. suggested that positive psychological interventions could also enhance wellbeing and life satisfaction [226].

Besides psychologic interventions, cognitive training seems to have positive impact on QoL in older people, as Noble et al showed in another metanalysis [227].

Another creative way of QoL improvement is an intergenerational attempt in which young and old persons practiced reminiscence together [228].

A problem in measurement of subjective outcomes over time, in this case the improvement of QoL after interventions, is response shift [229]. Changes in individual evaluation standards may lead to assumed variation of HRQoL over time. An example is rating one's health state by comparison to a roommate in hospital. Comparing oneself to somebody who is bedridden or terminally ill might change evaluation standards to a better perception of one's own situation. After discharge, the same patient might compare his situation with peers of the same age, who have higher functional capacities and therefore rate his HRQoL lower than before, even though the personal conditions remained stable. When evaluating interventions improving HRQoL, such interactions should be taken account of, otherwise, potential biases can occur [229].

Determinants of active and healthy aging require more attendance in future research and actions need to be designed to promote those determinants [230].

5.3 Frailty intervention – „Altersmedizinische Komplexbehandlung“

The consequence of detecting frailty by means of a CGA should be a geriatric treatment in order to improve outcomes and QoL of complex geriatric patients with several clinical syndromes [7].

A main problem in the development of effective therapy approaches is the persisting lack of mechanistic understanding, why results of a CGA are strongly correlated with negative outcomes. Translation of gathered information into treatment strategies remain a gap of knowledge, which should be faced by future researchers [7].

There is a lack of studies concerning interventions to improve frailty. The “Lancet frailty series” 2019 described only screening interventions in orthogeriatrics and cardiology [43] without naming

treatment interventions. Puts et al. reviewed studies in which frailty should be prevented or reduced. They showed that frailty could significantly be reduced by physical activity interventions and prehabilitation [231].

In Germany, the “Altersmedizinische Komplexbehandlung”, meaning individualised multidimensional intervention, is a potential way to combine acute internal medicine and elements of geriatric rehabilitation.

This treatment is conducted by a geriatric team as described in the introduction section, consisting of internal medicine and geriatric doctors, specialized nurses, physiotherapists, occupational and speech therapists, the social services and a pharmacist.

Patients stay at least two weeks in order to conduct twenty therapy sessions with physiotherapists and occupational therapists (on average two per day) and to have enough time for treatment of acute medical issues like, e.g., pneumonia, urinary tract infections or cardiac decompensation in heart insufficient patients.

Before the implementation of the geriatric ward “Universitäre Altersmedizin” at the University Hospital of Cologne, the complex treatment was conducted on individual patients at the nephrological unit. Müller et al. could prove that this treatment could significantly improve the MPI of those patients. Particularly pre-frail and frail patients had a higher benefit [14].

Potential improvements in patient-reported outcomes were not supervised in Müller’s study.

Patients on the geriatric ward “Universitäre Altersmedizin” were scientifically accompanied by study members of Ageing Clinical Research of the University Hospital of Cologne. Besides the standardized admission- and discharge tests conducted by the geriatric team, doctoral candidates added a CGA using the MPI, collection of GR and GS as well as asking for HRQoL using the EQ-5D. Meyer et al. compared those patients undergoing rehabilitative care with a historic control group, which included patients of the underlying study MPI-InGAH. They could prove that rehabilitative care improved multidimensional frailty and functional abilities at discharge [232], which led to a lower count of rehospitalisations and even lower mortality in a follow-up period of six months [232].

Those results show clearly the benefit of tailored geriatric treatments: Addressing patients at risk for severe outcomes with targeted geriatric intervention improved the prognosis of these patients.

Even if no specialised geriatric ward is available, the conduction of the multidimensional geriatric treatment on an internal ward leads to improved prognosis of pre-frail and frail patients [14]. Considering the large number of geriatric patients in internal medicine, geriatric treatment also should be provided outside geriatric hospitals.

The aim is to implement frailty-guided clinical care in all health care settings with focus on research about potential benefits, treatment strategies and clinical management [59].

5.3.1. Integrated care for older people “ICOPE”

In 2019, the WHO published a handbook called “Guidance on person-centred assessment and pathways in primary care”, which has the aim to improve healthy aging by focussing on intrinsic capacity [233]. Intrinsic capacity means the combination of physical and mental capacities of an individual. The interaction between intrinsic capacity and the environment and personal habits is called functional ability [233].

The core of this concept is to assess a person’s values, priorities, individual needs and goals in his/her social context. Six domains, which are known as priority conditions to decline intrinsic capacity are therefore screened: cognitive decline, limited mobility, malnutrition, visual impairment, hearing loss and depression [234].

Each condition is provided by recommended further assessments and procedures. Using these assessments, a personalized care plan should be developed and coordinated services spring into action with the goal of maintaining intrinsic capacity.

By providing step-by-step guidance, all medical and care disciplines could use this handbook correctly. Thanks to the screening tool, a first impression can be made in a manageable time slot, and further assessments are conducted only for impaired domains.

The ICOPE might be a supplementation to a CGA as it includes its new aspect of intrinsic capacity. Moreover, the ICOPE gives advises for further assessments and management to improve the intrinsic capacity. However, those treatment strategies are very general and still target personal limitations instead of promotion of resources.

Studies on the validity and feasibility of the screening tool are pending. An initial review of Pelegrim de Oliveira was not yet able to postulate sufficient evidence [234].

5.4 Addressing geriatric syndromes

Since a higher number of GS is associated with reduced prognosis according to the MPI [134] as well as with lower HRQoL, reduction of GS could potentially improve clinical outcomes. Geriatric medicine focusses on individual conditions like geriatric gyndromes besides standard medical treatment. Considering two examples, the tailored treatment of GS should be demonstrated now.

5.4.1. Polypharmacy

Polypharmacy is a very common GS, not only in our study cohort, where 57% percent of all patients had this syndrome. In Germany, about 42% of patients older than 65 years had polypharmacy [235]. There are different cut-offs for polypharmacy, a systematic review found 134 definitions [236]. We used nine or more drugs as threshold value. Other authors define

polypharmacy if more than five drugs are taken [236]. Using this definition, 83% of our included patients had polypharmacy.

Several studies proved the negative impact of polypharmacy on HRQoL [237–239]. Moreover, polypharmacy in older age leads to multiple adverse outcomes like falls, functional decline, adverse drug events, cognitive impairment, and even higher mortality [236,240–243].

Polymedication might not be inadequate per definition, regarding pharmacologic therapy of chronic heart failure with reduced ejection fraction, four drug classes (renin-angiotensin system inhibition, beta blockers, mineralocorticoid receptor antagonists and sodium-glucose transport protein 2 (SGLT2) inhibitors) showed evidence to bring prognostic benefit as reduced rate of hospital admission and reduced mortality [244]. Adding diuretic drugs in case of cardiac decompensation and e.g. antithrombotic drugs in case of comorbidities like atrial fibrillation or coronary heart disease, those patients automatically reach more than five drugs although only one organ system is treated according to general guidelines. Therefore, the focus has to be on inadequate medication in older people. Typical drugs of this category are cardiovascular drugs, sedatives, antidepressants and anticholinergics [235]. Especially drugs with anticholinergic or sedative effects should be banned as they increase the risk of falling and worse cognitive decline [243].

Besides the potential risks of polymedication for functional and cognitive decline, frail elders have a higher risk for receiving potentially inadequate medication in the future [245] which seems to be a vicious cycle of frailty and polypharmacy.

In Germany, some tools were developed to help avoiding inadequate medication. One of them is the “FORTA- Fit fOR The Aged classification”. This classification includes positive and negative advises for single drugs and drug categories in context of diagnoses. Four advises are made, ranging from “A = indispensable, B = benefcial, C = questionable, to D = avoid” [141,246]. Using the FORTA-classification, the frequency of adverse drug reaction could significantly be reduced. Moreover, activities of daily living improved significantly [247].

Another tool for identification of potentially inadequate medication is the START/STOPP screening tool. A review of Taylor et al proved effectiveness of this tool in reduction of falls, delirium, length of hospital stay and medication costs [248]. Other endpoints like mortality and quality of life were not significantly improved [248].

Using such classifications might help the clinicians in deprescribing and therefore reduce inadequate medication and polymedication. Further studies, especially those using the FORTA-classification, might support the positive results and maybe also improve mortality and QoL.

5.4.2. Instability

Besides physical injury, falls also have psychological consequences, especially evoking fear of falling. Studies showed that about 50% of people who fell down experience fear of falling [249]. Together, physical and mental harms may lead to increased disability, reduced independence and higher care needs which in consequence might affect people's quality of life as well [250]. The individual risk for future falls can be measured by some functional measures, best evidence is given for Berg Balance Scale, Timed Up and Go time and 5 times sit-to-stand [251]. Adding further measures like geriatric depression scale or Falls Efficacy Scale International (FES-I), the level of risk can be substantiated [251].

Regarding only fear of falling, a review by Schoene et al described an association between fear of falling and quality of life independently of conceptualisation of both terms.

This association remained significant even after adjusting for falls [250]. Due to its immense impact on QoL, instability or fear of falling should be recognised as crucial geriatric syndromes. Falls themselves may be reduced by different interventions. Frequency of falls could be lowered by a multidimensional intervention, improving extrinsic risk factors like shoes, surfaces and lighting [252]. Regarding fear of falling, a review of studies using physical exercises in community-dwelling elders could prove only a small effect on fear of falling immediately after the intervention [253]. Another study group designed a cognitive-behavioural therapy (STRIDE-study) which showed a significant improvement in different fear-of-falling and depression scores. Despite their expectations, other outcomes like quality of life, physical function and social participation could not be improved by the psychologic intervention [254].

A metanalysis of Weber et al showed that mind-body interventions could improve both fear of falling and QoL [224].

Further studies combining cognitive and physical interventions could show effects on both domains, falls and fear of falling, and therefore maybe improve other relevant outcomes like QoL.

5.5 Models of improved home transition

Frailty is a major risk factor for higher use and cost of healthcare as well as for negative outcomes like rehospitalisation and falls [38]. In order to reduce costs, the rate of rehospitalisation of frail elderly should be minimised. Different study groups investigated the benefit of new concepts of home-transition. At the Universitäre Altersmedizin at the University hospital of Cologne, Meyer et al. focussed on incorporation of the general practitioner as well as in-hospital training exercises, which should be conducted at home, as well. Moreover, a guidebook on healthy aging was given to the patient. The study group could not prove effects on rehospitalisation days in the follow-up period of six months, but multidimensional prognosis

improved at discharge and self-esteem and mood could be positively affected [232]. HRQoL using the EQ-5D-5L was not significantly improved, but trends towards an increased QoL were shown [232].
A systematic review of 2020 by Morkisch et al. included three studies using a transitional care model for patients older than 65 years and showed also mixed results in the rate of readmission (two positive studies, one without effect on readmission rates) [255].

Another approach is the TIGER-study, which took place between 2018 and 2019 in Regensburg, Germany. Here, individual care planning was conducted according to patient's needs and personal visits as well as telephone contacts took place over a time of 12 months after discharge. The primary outcome was readmission-rate, second outcomes were HRQoL, quality of care and mobility [256]. Results are not published to date.

A third example of home transition studies is the "Elipfad" study, which was started in September 2023 at six hospitals in Northrhine-Westphalia, Germany. It is a randomised controlled trial with the aim to reduce readmission rates of older, multimorbid patients. Inclusion criteria are age >55 years, multimorbidity (3 or more chronic diseases) and having at least one diagnosis like heart failure, kidney failure, chronic obstructive lung disease, diabetes mellitus type 2, peripheral artery disease, coronary heart disease or arterial hypertension [257].
In-hospital therapy does not differ between intervention and control group. Regarding discharge, in the intervention group, a casemanager contacts the general practitioner and supports the patient in upcoming questions. Additionally, each patient receives a smart assistant, meaning a tablet, for six weeks after discharge. Here, personalised training videos are stored as well as information on the patient's medication and diseases. Moreover, patients should insert their vital signs like blood pressure and weight into the tablet. The casemanager can check this data and contact the general doctor at an early stage in case of disturbance [258]. Since the study is still in recruitment status, there is no data available considering the effects of this concept.
As described in this section, improved home transition and prevention of hospital admissions are current research topics, which have only small evidence to date with heterogenous results. Nevertheless, such studies are extremely important regarding the rising number of geriatric patients flooding the health system [2]. We therefore urgently need further concepts and studies to reduce the burden of repetitive hospitalisations.

5.6 Research outlook

5.6.1. AEQUI study

“AEQUI – The Aged European population: QUality of life and Infectious diseases” is a European study which investigated the impact of airway infections and bloodstream infections on quality of life in older patients. The multicentre study took place in Italy, Spain, France and Germany and was conducted between 2020 and 2024. In Germany, the University Hospital of Cologne under direction of Prof. Priv.-Doz. Dr. Dr. Polidori-Nelles supervised the German study group, which was located at Cologne, Mannheim, Göttingen and Lemgo.

The study design was similar to the MPI-InGAH study: Patients older than 65 years who were hospitalised due to airway infections (upper airway infection with fever or lower airway infections) or patients with bloodstream infections were screened an included if signing informed consent and agreeing to follow-up phone calls. Terminally ill, bed-ridden and severely disabled patients were excluded. Besides a Comprehensive Geriatric Assessment, using the Multidimensional Prognostic Index, the EQ-3L questionnaire was used.

Furthermore, laboratory results were analysed. After three and six months after discharge, telephone follow-up calls were conducted in order to ask for rehospitalisations and quality of life. After six months, another telephone version on the MPI was performed.

Patients included into the control group had no acute infection and were hospitalised due to other medical reasons. The aim was to find out whether infectious diseases affect QoL of older in-patients more than other reasons. Therefore, changes in QoL from baseline to FU were analysed. This study will help understand how different types of diseases influence patient’s wellbeing and perception of quality of life and tries to give insight in the mechanisms of these influence. Since the study has been completed quite recently, the publication of the results is still in progress [259].

5.6.2. Cologne database

Over the past eight years, the study group Aging Clinical Research Cologne under the direction of Prof. Prov.-Doz. Dr. Dr. Polidori-Nelles included more than 3,000 patients into their studies. All these patients underwent a CGA using the Multidimensional Prognostic Index and geriatric syndromes and resources. Moreover, descriptive data like length of stay, grade of care and living conditions were systematically described. Quality of life was collected in about one third of all patients. Follow-up periods varied from six months to more than two years.

Patients were recruited in different settings, e.g. at the general doctor’s and geriatric clinics, but mostly at the University Hospital of Cologne. About half of the patients were recruited from the emergency department, the other half from wards of internal medicine, either with cardiac, nephrological or geriatric focus.

Regarding the robustness of statistical results, this cohort has big potential for further analyses. On the one hand, economic factors such as length of hospital stay, complications and care needs can be analysed and on the other hand, patient-reported outcomes such as quality of life and wellbeing in different settings and under different treatment strategies (usual care vs. geriatric treatment) could be compared.

5.7 Conclusion

This work illustrated the plurality of influencing factors and associations of health-related quality of life and results of a Comprehensive Geriatric Assessment, including geriatric syndromes and resources.

Those results make clear that traditional outcomes like mortality and changes in health state cannot be considered without the involvement of also patient- reported outcomes. Subjective aspects of patients should be taken into account in order to complete the CGA by means of the patients' individual value systems and expectations.

Health-related quality of life is an outcome that emphasises the subjective perception of illness and health. The present study showed strong interrelations between HRQoL and geriatric conditions, captured by the CGA. In light of increasing hospitalisation rates, HRQoL seems to be suitable as an outcome marker for inpatients undergoing high performance medicine. Independently of the health care setting, HRQoL might become a fundamental tool to improve health status and therefore reduce rehospitalisation rates.

The multidimensional assessment of health-related quality of life also records coping factors and resources that patients use to deal with acute and chronic illness. By structured record of geriatric resources the deficit-focussed investigation will be complemented and balancing factors of geriatric syndromes will be shown up [2].

Research has to overcome its restraint to only describing and cataloguing contributors to health and wellbeing. By systematic adoption of HRQol-evaluation, health status and quality of life might be improved since identification and activation of personal resources enable patients to achieve positive outcomes [4].

When planning and conducting future treatment strategies, clinicians should always incorporate individual preferences and needs. Likewise, focus must be placed on the promotion of personal resources to overcome the traditional and so often insufficient strategy, which tries to intervene multiple deficits separately. The focus has to be shifted from disease to functioning and towards a focus on intrinsic capacity [2].

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7. Appendix

7.1 List of figures

Fig. 1: The three dimensions of frailty according to Ferruci et al.

Fig. 2: The Clinical Frailty Scale

Fig. 3: The Chapo Model

Fig. 4: The interconnected relationship between a patient's state of health, quality of life, and health-related quality of life according to Vetter et al

7.2 List of tables

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Table 2: P-values: comparison of HRQoL by GS and GR

Table 3: Spearman-correlation coefficients of inhospital CGA and Follow-up-HRQoL/survival days

Table 4: Comparison of HRQoL by disease severity groups, measured by CIRS (p-values)

7.3 List of publications

7.3.1. As first author

o Paper: Heeß A, Meyer AM, Becker I, Noetzel N, Verleysdonk J, Rarek M, Benzing T, Polidori MC. The prognostic fingerprint of quality of life in older inpatients : Relationship to geriatric syndromes' and resources' profile. Z Gerontol Geriatr. 2022 Feb;55(1):38-43. English. doi: 10.1007/s00391-021-01978-5. Epub 2021 Oct 6. PMID: 34617144.

o Poster DGG 2019: Comprehensive Geriatric Assessment-basierte Prognoseberechnung und subjektive Lebensqualität älterer hospitalisierter Patienten

o Abstract DGIM 2020: Kann ein Comprehensive Geriatric Assessment auch Aussage über die subjektive Lebensqualität von hospitalisierten, älteren Patienten treffen?

7.3.2. As co-author

Role of a multidimensional prognosis in-hospital monitoring for older patients with prolonged stay.

Pickert L, Meyer AM, Becker I, **Heeß A**, Noetzel N, Brinkkötter P, Pilotto A, Benzing T, Polidori MC.Int J Clin Pract. 2021 May;75(5):e13989. doi: 10.1111/ijcp.13989. Epub 2021 Feb 1.PMID: 33406298

The impact of oral health on prognosis of older multimorbid inpatients: the 6-month follow up MPI oral health study (MPIOH).

Noetzel N, Meyer AM, Siri G, Pickert L, **Heeß A**, Verleysdonk J, Benzing T, Pilotto A, Barbe AG, Polidori MC.Eur Geriatr Med. 2021 Apr;12(2):263-273. doi: 10.1007/s41999-020-00427-7. Epub 2020 Nov 18.PMID: 33206351

Prognostic Signature of Chronic Kidney Disease in Advanced Age: Secondary Analysis from the InGAH Study with One-Year Follow-Up.

Meyer AM, Pickert L, **Heeß A**, Becker I, Kurschat C, Bartram MP, Benzing T, Polidori MC. Biomolecules. 2022 Mar 9;12(3):423. doi: 10.3390/biom12030423.PMID: 35327615

An interdisciplinary intervention is associated with overall improvement of older inpatients in a non-geriatric setting: A retrospective analysis of an observational, longitudinal study with one-year follow up

Franziska M. Müller, Anna M. Meyer, Lena Pickert, **Annika Heeß**, Ingrid Becker, Thomas Benzing,1 M. Cristina Polidori

Geriatric Care 2021; 7:9723 doi:10.4081/gc.2021.9723

Prognostic signature of multimorbidity, geriatric syndromes and resources cluster in older in- and outpatients: a pooled secondary analysis with a 6-month follow-up.

Jill Stegemann, Anna Maria Affeldt, Luisa Mück, Anne Ferring, Laura Gerhards, Lena Pickert, **Annika Bausch**, Thomas Benzing, Philipp Antczak, M Cristina Polidori

BMJ Open 2024;14:e086975. doi:10.1136/ bmjopen-2024-086975

Measuring the impact of hospitalisation for infectious diseases on the quality of life of older patients in four European countries: the AEQUI longitudinal matched cohort study (2020-2023)

Veronese, Nicola; Polidori, Maria Cristina ; Maggi, Stefania; Zamora , Javier ; Ruiz Calvo, Gabriel; Bangert, Mathieu; Bourron, Pierre; **Bausch, Annika**; Avilés-Hernández, Juan Dionisio; López-Soto, Alfonso; Padrón Guillén, Daniel; Lanoix, Jean Philippe; Cruz-Jentoft, Alfonso José; Gavazzi, Gaëtan

submitted in Clinical Microbiology and Infection, December 2024

8. Pre-publication of results

8.1 Published original work

Heeß A, Meyer AM, Becker I, Noetzel N, Verleysdonk J, Rarek M, Benzing T, Polidori MC. The prognostic fingerprint of quality of life in older inpatients : Relationship to geriatric syndromes' and resources' profile. Z Gerontol Geriatr. 2022 Feb;55(1):38-43. English. doi: 10.1007/s00391-021-01978-5. Epub 2021 Oct 6. PMID: 34617144.

8.2 Poster presentation: 31. Jahreskongress der deutschen Gesellschaft für Geriatrie und Gerontologie 2019

Comprehensive Geriatric Assessment-basierte Prognoseberechnung und subjektive Lebensqualität älterer hospitalisierter Patienten

Annika Heeß, Lena Pickert, Anna Maria Meyer, Ingrid Becker,Franziska Müller, Nicolas Noetzel, Alberto Pilotto, Thomas Benzing und Maria Cristina Polidori

8.3 Accepted abstract: 126. Kongress der Deutschen Gesellschaft für Innere Medizin 2020

Kann ein Comprehensive Geriatric Assessment auch Aussage über die subjektive Lebensqualität von hospitalisierten, älteren Patienten treffen?

Annika Heeß, Lena Pickert, Anna Maria Meyer, Ingrid Becker, Volker Burst, Nicolas Noetzel, Joshua Verleystonk, Paul Brinkkötter, Alberto Pilotto, Thomas Benzing und Maria Cristina Polidori