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ORIGINAL ARTICLE
Special populations

Heart failure and dementia: a comparative analysis with different types of cancer

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Aims The prognosis and quality of life of patients with heart failure (HF) is determined by comorbidities, with dementia/cognitive decline believed to have a significant impact in this regard. This study compares the incidence of dementia in patients with HF with that in patients with common cancers in a large collective of outpatients.

Methods and results This retrospective cohort study assessed the incidence of dementia/cognitive decline [International Classification of Diseases, 10th revision (ICD-10): I50] in a cohort of patients ≥65 years diagnosed with HF (ICD-10: I50), breast cancer (ICD-10: C50), prostate cancer (ICD-10: C61), or digestive organ cancer (ICD-10: C15-C26) in 1274 German general practices between January 2000 and December 2018. Multivariable Cox regression models were used to study the association between HF and dementia compared to each of three cancer cohorts. We included 72 259 patients with HF, 10 310 patients with breast cancer, 12 477 patients with prostate cancer, and 12 136 patients with digestive organ cancer. A total of 27.8% of patients with HF were diagnosed with dementia during the 10-year observation period compared to 16.2% of patients with breast cancer, 18.6% of patients with digestive organ cancer, and 16.1% of patients with prostate cancer. Patients with HF were significantly more likely to develop dementia within 10 years after diagnosis than patients with breast cancer [hazard ratio (HR): 1.36 (95% confidence interval 1.28–1.45, $P < 0.001$], prostate cancer [HR 1.38 (1.130–1.47), $P < 0.001$], or gastrointestinal tumours [HR 1.31 (1.24–1.39), $P < 0.001$].

Conclusions Our study demonstrates the significance of dementia in patients with HF, in whom the condition is much more prevalent than in patients with cancer.

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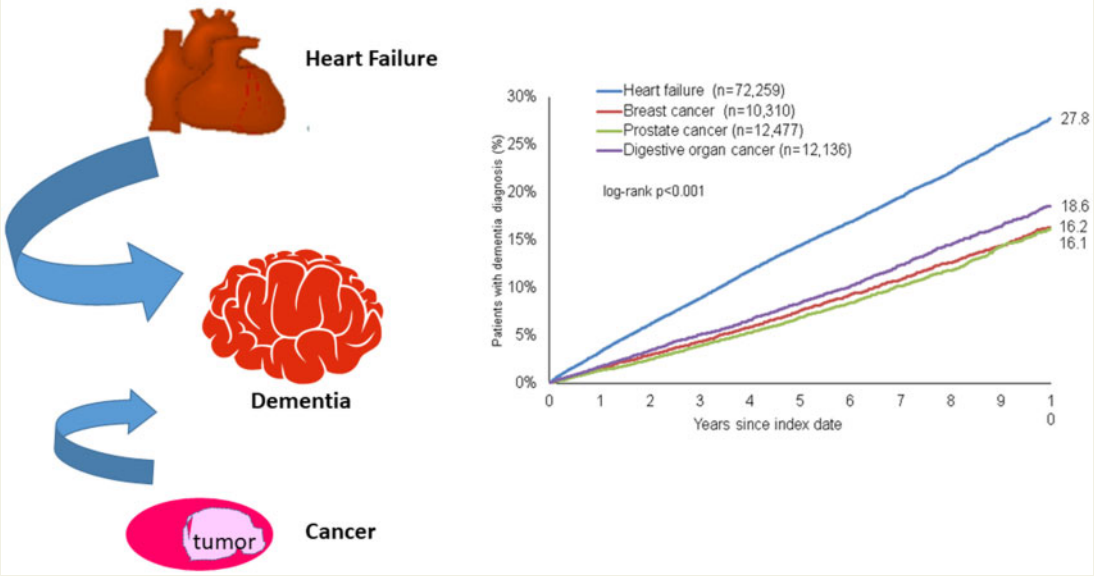
Graphical Abstract



Keywords Heart failure • Comorbidities • Dementia • Cancer

Introduction

Heart failure (HF) is a heavy burden for the healthcare system and affected patients alike, and comorbidities are a significant aggravating factor, affecting both prognosis and quality of life.[1] In Western Europe, patients already have an average of five comorbidities at the time of diagnosis.[2] In this context, HF resembles malignant oncological diseases, where comorbidities also play a major role.[3] Like HF and cancer, dementia is one of the most burdensome diseases in Western countries.[4,5] A number of recent studies have linked dementia and HF.[4,5] As with HF, the incidence of dementia continues to rise,[6] but the precise nature of the relationship between the two diseases remains unclear. A Danish study showed that patients with HF had an ~21% higher risk of developing dementia,[4] while a smaller study showed a twofold higher risk of developing dementia or Alzheimer's disease in older patients with HF.[7,8] Possible causes for the increased co-incidence of HF and dementia have not yet been clearly defined. While the direct neurotoxic effects of oncological therapies have also been described as a cause of increased dementia rates in patients with cancer,[9] this effect has not been identified in patients with HF. The present study of a large cohort of outpatients assessed the incidence of dementia during the course of HF and compared it with the incidence of dementia in patients with several common cancers.

Methods

Database

This study was based on data from the Disease Analyzer database (IQVIA), which contains drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists.[10] The database covers ~3% of all outpatient practices in Germany. Diagnoses [according to International Classification of Diseases, 10th revision (ICD-10)], prescriptions [according to Anatomical Therapeutic Chemical (ATC) Classification system], and the quality of reported data are monitored regularly by IQVIA. In Germany, the sampling methods used to select physicians' practices are appropriate for obtaining a representative database of general and specialized practices. It has previously been shown that the panel of practices included in the Disease Analyzer database is the representative of general and specialized practices in Germany[11] For example, Rathmann *et al.*[11] demonstrated that there was good correlation between the outpatient DA database with German reference data with respect to the incidence or prevalence of cancer diagnoses. Finally, this database has already been used in previous studies focusing on both cardiovascular disorders[12] and cancer.[13,14]

Study population

This retrospective cohort study included patients aged ≥65 years with an initial diagnosis of HF (ICD-10: I50), breast cancer (ICD-10: C50),

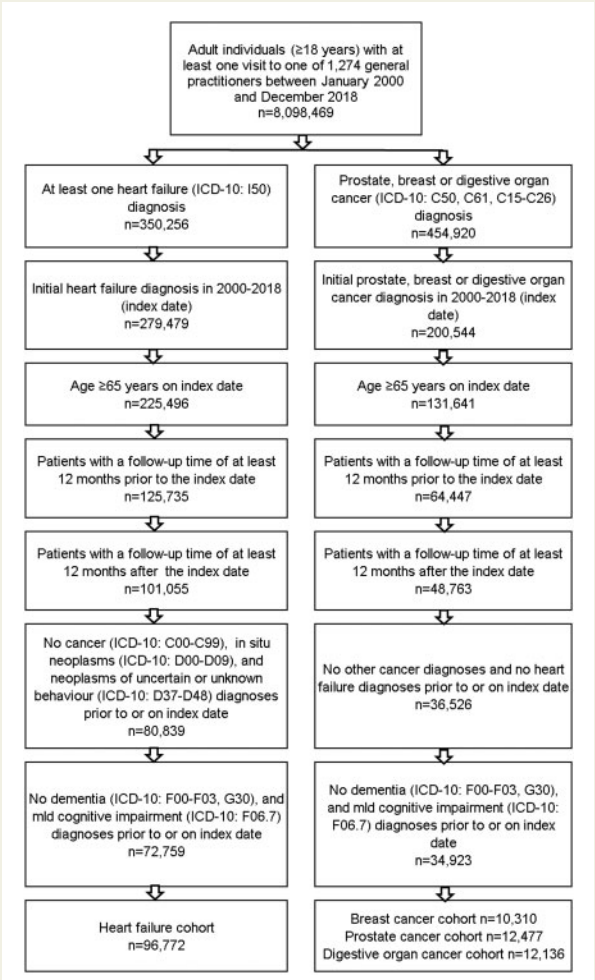


Figure 1 Selection of study patients.

prostate cancer (ICD-10: C61), or digestive organ cancer (ICD-10: C15–C26) in 1,274 general practices in Germany between January 2000 and December 2018 (index date; *Figure 1*). One further inclusion criterion was an observation time of at least 12 months prior to the index date and at least 12 months after the index date. Patients with cancer diagnoses (ICD-10: C00–C99), *in situ* neoplasms (ICD-10: D00–D09), or neoplasms of uncertain or unknown behavior (ICD-10: D37–D48) prior to the index date were excluded from the HF cohort, while patients with other cancer diagnoses or HF prior to the index date were excluded from the cancer cohorts (*Figure 1*). Furthermore, patients with diagnoses of dementia (ICD-10: F00–F03, G30) or mild cognitive impairment (ICD-10: F06.7) prior to the index date were excluded to allow for the estimation of incident diagnoses of these psychiatric diseases after the index date.

Study outcomes and covariates

The main outcome of the study was the incidence of dementia among patients with HF compared to that in patients with cancer. As >80% of patients with dementia have unspecified dementia (ICD-10: F03), all dementia types were analysed as a compound effect.

Statistical analyses

Differences in the sample characteristics between patients with HF and those with breast, prostate, or digestive organ cancer were tested using chi-squared tests for categorical variables and Kruskal–Wallis tests for continuous variables. In addition to age and sex, cohorts were compared in terms of several comorbidities documented within 12 months prior to the index date: diabetes mellitus (ICD-10: E10–14), obesity (ICD-10: E66), hypertension (ICD-10: I10), lipid metabolism disorders (ICD-10: E78), peripheral artery disease (ICD-10: I70.2, I73.9), myocardial infarction (ICD-10: I21–I23, I25.2), stroke incl. transient ischemic attack (TIA) (ICD-10: I63, I64, G45), depression (ICD-10: F32, F33), and osteoporosis (ICD-10: M80, M81). The cumulative incidence of dementia within 10 years after the index date was evaluated using Kaplan–Meier curves. A follow-up period of 10 years was chosen to take into account the high mortality of the investigated diseases of HF, cancer, and dementia and ensure sufficient follow-up time to show statistical effects. Multivariable Cox regression models were used to study the association between HF and dementia as compared to each of three cancer cohorts, adjusted for age, sex, and comorbidities. These models were produced separately for five age groups (65–70, 71–75, 76–80, 81–85, and >85 years) as well as women and men (for the comparison of HF with digestive organ cancer).

A sensitivity analysis with matched pairs was performed to avoid possible residual confounding. Matching was based on a propensity score that was constructed as the conditional probability of having HF as a function of age, sex, and comorbidities (diabetes, obesity, hypertension, lipid metabolism disorders, peripheral artery disease, myocardial infarction, stroke incl. TIA, depression, and osteoporosis). Greedy matching was used by choosing a patient with HF whose propensity score was closest to that of a randomly selected patient with cancer for matching. Finally, univariate Cox regression models were used.

As patients with HF can develop cancer, and patients with cancer can develop HF during the follow-up,[15,16] we performed a further sensitivity analysis comparing the effect of HF plus cancer vs. cancer alone using Cox regression analysis. *P*-values <0.05 were considered statistically significant. Analyses were carried out using SAS version 9.4 (SAS institute, Cary, USA). This study was performed in accordance with the guidelines for Good Practice of Secondary Data Analysis.[17]

Ethical standards

Only aggregated, anonymized patient data were used in these analyses. This study was performed in accordance with the Declaration of Helsinki, the guidelines for Good Practice of Secondary Data Analysis,[17] and the ICMJE Recommendations for the Conduct, Reporting Editing and Publication of Scholarly Work in Medical Journals. Since only anonymized data were used, which could not be traced back to individual persons, the research protocol did not have to be approved by the local ethics committee, and it was not necessary to obtain informed consent from individual patients to participate in the study. This was confirmed by the local ethics committee of the Christian-Albrechts-University (CAU) of Kiel, Kiel, Germany (File reference D413/21).

Results

The basic characteristics of the study groups are displayed in *Table 1*. The study included 72 259 patients with HF, 10 310 patients with breast cancer, 12 477 patients with prostate cancer, and 12 136 patients with cancer of digestive organs. The mean ages of the patient groups differed somewhat: 76.8 [standard deviation (SD) 6.7] for patients with HF vs. 73.5 (SD 6.3) years for patients with breast cancer vs. 73.6 (SD 5.6) years for those with prostate cancer and 74.5

Table 1 Basic characteristics of the study sample

Variable	Proportion affected among patients with heart failure (%), *N* = 72 259	Proportion affected among patients with breast cancer (%), *N* = 10 310	Proportion affected among patients with prostate cancer (%), *N* = 12 477	Proportion affected among patients with digestive organ cancer (%), *N* = 12 136	*P*-value
Age (mean, SD)	76.8 (6.7)	73.5 (6.3)	73.6 (5.6)	74.5 (6.2)	<0.001
Age 65–70	20.5	38.4	33.7	30.3	<0.001
Age 71–75	23.0	26.5	31.3	27.8	
Age 76–80	26.3	20.3	22.3	24.0	
Age 81–85	19.2	10.1	9.8	12.5	
Age >85	11.0	4.7	2.9	5.4	
Women	56.8	100	0	46.8	<0.001
Men	43.2	0	100	53.2	
Comorbidities documented within 12 months prior to index date					
Diabetes	39.1	23.7	26.4	31.2	<0.001
Obesity	15.9	10.4	8.2	10.7	<0.001
Hypertension	79.7	64.7	64.9	66.3	<0.001
Lipid metabolism disorders	49.0	42.0	45.7	43.2	<0.001
Peripheral artery disease	10.9	3.8	6.7	7.2	<0.001
Myocardial infarction	5.8	1.4	3.4	2.8	<0.001
Stroke incl. TIA	9.8	4.6	6.3	6.6	<0.001
Depression	19.9	20.3	10.0	15.3	<0.001
Osteoporosis	13.7	16.1	3.6	9.9	<0.001

Proportions of patients in % given, unless otherwise indicated.
SD, standard deviation.

(6.2) years for patients with gastrointestinal tumours. Comorbidities documented within 12 months prior to the index date that may influence the incidence of dementia are distributed according to *Table 1*.

A total of 27.8% of patients with HF were diagnosed with dementia within 10 years after the index date compared to 16.2% of patients with breast cancer, 18.6% of patients with cancer of digestive organs, and 16.1% of patients with prostate cancer (*Figure 2*).

The application of multivariate Cox regression models showed that patients with HF were significantly more likely to develop dementia within 10 years after diagnosis than patients with breast cancer [hazard ratio (HR): 1.36 (95% confidence interval 1.28–1.45, $P < 0.001$)]. Comparing different age groups, the only significant difference was found in patients who were 80 years old or younger (*Table 2*). Compared to those with prostate cancer, the likelihood of developing dementia was also significantly increased in patients with HF [HR 1.38 (1.30–1.47), $P < 0.001$]. This difference was significant in all age groups except for patients older than 85 years. Furthermore, the likelihood of dementia was significantly higher in patients with HF than in those with gastrointestinal tumours [HR 1.31 (1.24–1.39), $P < 0.001$]. This finding was similar for both sexes and across all age groups except for patients older than 80 years ($N = 6351$); 8.8% of the HF cohort received a cancer diagnosis during the follow-up. The interaction effect was as follows: HR 1.48 (1.37–1.59), $P < 0.001$ for HF plus breast cancer vs. breast cancer alone, HR 1.54 (1.44–1.65), $P < 0.001$ for HF plus prostate cancer vs. prostate cancer alone, and HR 1.50 (1.41–1.61), $P < 0.001$ for HF plus gastrointestinal tumours vs. gastrointestinal tumours alone.

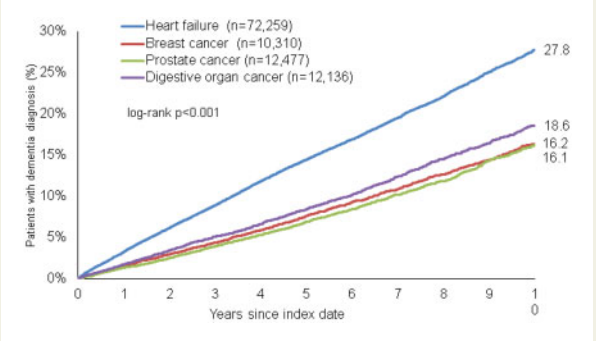


Figure 2 Ten-year cumulative incidence of dementia diagnosis in patients with heart failure vs. patients with breast, prostate, or digestive organ cancer.

Hazard ratios were similar in sensitivity analyses based on matched pairs: HR 1.39 (1.30–1.49), $P < 0.001$ for HF vs. breast cancer, HR 1.46 (1.37–1.56), $P < 0.001$ for HF vs. prostate cancer, and HR 1.22 (1.15–1.30), $P < 0.001$ for HF vs. gastrointestinal tumours.

Table 2 Comparison of heart failure and cancer diagnoses in terms of incident dementia diagnosis within 5 years of index date in patients followed in general practices in Germany (Cox regression models)

Variable	Hazard ratio (95% CI)a	*P*-value
Heart failure vs. breast cancer (women)	1,36 (1.28–1.45)	<0.001
Age ≤70	1.48 (1.29–1.71)	<0.001
Age 71–75	1.49 (1.31–1.69)	<0.001
Age 76–80	1.30 (1.15–1.47)	<0.001
Age 81–85	1.12 (0.97–1.29)	0.116
Age >85	1.09 (0.90–1.33)	0.381
Heart failure vs. prostate cancer (men)	1.38 (1.30–1.47)	<0.001
Age ≤70	1.46 (1.27–1.67)	<0.001
Age 71–75	1.45 (1.30–1.62)	<0.001
Age 76–80	1.22 (1.10–1.36)	<0.001
Age 81–85	1.34 (1.16–1.56)	<0.001
Age >85	1.30 (1.01–1.67)	0.040
Heart failure vs. digestive organ cancer	1.31 (1.24–1.39)	<0.001
Age ≤70	1.31 81.14–1.52)	<0.001
Age 71–75	1.22 (1.09–1.36)	<0.001
Age 76–80	1.45 (1.30–1.62)	<0.001
Age 81–85	1.16 (1.03–1.31)	0.018
Age >85	1.36 (1.12–1.64)	0.002
Women	1.29 (1.19–1.39)	<0.001
Men	1.34 (1.23–1.46)	<0.001

[a]Multivariable Cox regression adjusted for age, sex, and comorbidities (diabetes, obesity, hypertension, lipid metabolism disorders, peripheral artery disease, myocardial infarction, stroke incl. TIA, depression, and osteoporosis).

Discussion

Our study shows a significantly higher incidence of dementia in patients with HF than patients with any of the types of cancer analysed. This emphasizes the large scale of this problem, which is still underrepresented in the clinical care of patients with HF. Not only is the incidence of dementia increased in those with HF, but the condition also appears to significantly worsen the prognosis and quality of life of patients.[18,19]

What are the mechanisms that make patients with HF so vulnerable to cognitive decline? Low cardiac output can directly reduce blood flow to the heart, contributing to cerebral hypoperfusion and vascular autoregulation. The neurohumoral activation typical of HF can lead to generalized systemic inflammation and cerebral microvascular dysfunction. All these mechanisms may pave the way for chronic cerebral hypoxia and contribute directly to the pathogenesis of dementia.[20,21] There may be a close link between HF and vascular forms of dementia. Stroke is a strong risk factor for dementia.[22] The incidence of stroke is higher in our HF cohort than in the different cancer groups, which might in part have contributed to the increased dementia rate in this cohort. Risk factors such as small vessel disease are also especially common in patients with ischaemic heart disease.[23]

Other possible problems associated with dementia may include reduced ability to follow adequate HF therapy, resulting in further deterioration of the patient's cardiovascular status. A 'vicious circle' of increased cerebral hypoperfusion, further deterioration of cognitive abilities, and a loss of memory may develop.[23] HF and cancer may share some common pathophysiological risk factors for dementia. Indeed, the role of cardiovascular risk factors such as physical inactivity and obesity and arterial hypertension as risk factors for the onset of dementia is well established.[24] Smoking is also a risk factor for both HF and cancer, as well as for developing dementia.[25] Insofar as the strong statistical association between HF and the occurrence of dementia shown in our study can be causally explained, the extent to which a specific dementia-promoting pathophysiology of HF exists and the proportion caused by common risk factors remain speculative. As a possible pathophysiological explanation: both patients with HF and cancer may suffer from a state of chronic inflammation, which may in turn promote dementia.[9,23] Finally, our data also point to a particular problem shared by patients with HF, cancer, and dementia, namely that HF[26] and dementia, and to some extent cancer (especially prostate cancer[27]) are conditions that are associated with ageing patients in particular. The major, and as yet completely unresolved, problem of HF with preserved ejection fraction (HFpEF) is virtually defined as a disease of older patients and is known to be a disease with comorbidities.[28] The particular influence of frailty, which seems to play an important role in the development of dementia, should also be emphasized in this context.[26]

The fact that we only looked for the relatively unspecific diagnosis of dementia as a comparative diagnosis and not for specific subtypes such as Alzheimer's disease could be seen as a limitation of our study. Like HF, this disease is becoming increasingly widespread due to the ageing of the population, to the extent that that it is also referred to as the pandemic of the 21st century.[29] The exact nature of the connection between HF and Alzheimer's disease is not yet clear. For

some time now, there has been discussion of a connection between reduced cerebral perfusion, such as in HF, and the development of Alzheimer's.[30] New studies indicate that both diseases have a common pathophysiology through the 'metastatic' deposition of beta amyloid in the heart of patients with Alzheimer's disease, but also in patients with dilated cardiomyopathy.[31] This newly-discovered connection between the two diseases is certainly highly interesting and is currently the subject of further research.

One clear difference between cancer and HF in relation to dementia could be the impact of potential therapies. Chemotherapeutic treatment concepts in cancer care generally carry a risk of neurotoxic or neurodegenerative side effects.[9] In this respect, there is more hope in HF care that adequate, guideline-compliant therapy can also have a neuroprotective effect.[32] Caution must be exercised in individual cases, however, when using beta-blockers, for example. One concern regarding the use of the new highly effective substance valsartan/sacubitril was that inhibiting the degradation of b-amyloid may promote the aggregation of b-amyloid in the brain. To date, however, the large pivotal PARADIGM trial has not shown any increased rate of Alzheimer's/dementia from sacubitril/valsartan.[33] Therefore, it should still be assumed that it is HF that promotes the onset of dementia and that optimal HF therapy may be a means of preventing cognitive decline. Our database is mainly fed by input from general practitioners. Our data show the specific importance of general medical care or geriatric care for elderly patients with HF. GPs/geriatricians often know their patients over a longer period of time and are particularly well placed to recognize changes in their cognitive performance and to initiate appropriate measures for the diagnosis and supportive therapy where there is a possibility that the patient will develop dementia. General practitioners are of pivotal importance in the care of patients with HF in Germany.[34] They are at the center of patient care. The detection and treatment of comorbidities such as dementia show the strength of this system.

Our study is subject to a number of limitations. As in all epidemiological studies with a large population, our study may be affected by residual confounding.[35] As described above, we investigated associations with the relatively general diagnosis of dementia and not the specific subtypes such as Alzheimer's disease or Binswanger's disease (subcortical arteriosclerotic encephalopathy). Similarly, our database does not provide clear data on the treatment regimens followed by individual patients. For future association studies, it would be interesting to investigate differences between patients who received optimal treatment and patients with suboptimal HF therapy, for example. In addition, the individual study groups do not correspond exactly in the distribution of individual diseases such as obesity, which can of course also have an influence on the development of dementia. It should be noted that we are not presenting a case-control study but rather a cohort study A possible bias could arise from the misdiagnosis of HF in patients who actually died from dementia. Many patients with dementia live in nursing homes, where there seems to be a particular risk of misdiagnosis of HF.[36] Furthermore, all study diagnoses relied on ICD-10 codes filled in by primary care physicians only, and no diagnosis details or information on severity levels could be accessed. For example, stratification into hypertensive heart disease/HF with preserved ejection fraction (HFpEF) or reduced ejection fraction was not possible, which would have been desirable, especially given the special significance of HFpEF in advanced age[1] and the particular importance of comorbidities, most notably for the entity HFpEF.[37] Finally, our database does not contain any data on mortality or on the reason for loss of a patient to follow-up. We therefore cannot exclude the possibility that a longer life span of patients with HF vs. patients with cancer represents a bias related to the increased incidence of HF. However, it has already been shown that HF mortality tends to be higher than that of major cancers investigated in our study, such as female patients with HF vs. patients with breast cancer or male patients with HF vs. patients with prostate cancer.[38] A life span-related bias is therefore rather unlikely, at least in these comparison groups.

We believe that these possible disadvantages are compensated for by the large number of cases we can draw on, which allows us to present a very representative picture of the distribution of dementia in the individual disease groups.

In summary, dementia is a particularly important comorbidity in patients with HF, and is even more prevalent in these individuals than in those with major cancers. The care of ageing patients with HF must take this development into account to an even extent, especially if we wish to further extend the life span of this patient group. Cognitive decline detection programs need to be implemented much more often in care, a common task for all professionals involved in the care of patients with HF.

Lead author biography

Mark Luedde Training and residency at Heidelberg University Hospital, Germany and Christian-Albrechts University of Kiel, Germany. Research Interest: Heart Failure (Molecular and Clinical), Intensive Care Medicine. Clinical Interest: Heart Failure, Interventional Cardiology, Cardiac MRI, Intensive Care Medicine

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Data availibility

Data are available upon reasonable request.

Conflict of interest: The authors state that there is no conflict of interest.

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