

RELATIONSHIP BETWEEN QUALITY OF LIFE INDICATORS AND CARDIAC STATUS INDICATORS IN CHEMOTHERAPY PATIENTS

POVEZANOST MED KAZALNIKI KAKOVOSTI ŽIVLJENJA TER KAZALNIKI SRČNEGA STATUSA PRI BOLNIKI, KI PREJEMAJO KEMOTERAPIJO

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ABSTRACT

Aim: With the aim of improving personalized treatment of patients on chemotherapy, the objective of the study was to assess the degree of association between selected Quality of life (QoL) indicators and both clinical and imaging cardiac status indicators when detecting deterioration in QoL of these patients.

Keywords:

antineoplastic agents, cardiotoxicity, ventricular function - left, ventricular function - right, quality of life, magnetic resonance imaging, cine, echocardiography, lymphoma, Hodgkin disease, breast neoplasms

Methods: In a cohort clinical study in Hamburg, from August 2017 through October 2020, 59 cancer patients, aged 18-80 years, were evaluated before chemotherapy, and at several follow-ups, using EQ-5D and SF-36 QoL questionnaires, fast strain-encoded (fast-SENC) cardiac magnetic resonance (CMR), conventional CMR, and echocardiography, and further received a clinical and biomarker examination. Data was analyzed using survival analyses. A decline of more than 5% in each observed QoL metric value was defined as the observed event. Patient were separated into groups according to the presentation of cardiotoxicity as per its clinical definition, the establishment of the indication for cardioprotective therapy initiation, and by a worsening in the value of each observed imaging metric by more than 5% in the previous follow-up compared to the corresponding pre-chemotherapy baseline value.

Results: Among clinical cardiac status indicators, the indication for cardioprotective therapy showed statistically good association with QoL scores (EQ-5D $p=0.028$; SF-36 physical component $p=0.016$; SF-36 mental component $p=0.012$). In terms of imaging metrics, the MyoHealth segmental myocardial strain score was the only one demonstrating consistently good QoL score association (EQ-5D $p=0.005$; SF-36 physical component $p=0.056$; SF-36 mental component $p=0.002$).

Conclusions: Established fast-SENC CMR scores are capable of highlighting patients with reduced QoL, who require more frequent/optimal management.

IZVLEČEK

Namen: Z namenom izboljšati personalizirano zdravljenje bolnikov, ki prejemajo kemoterapijo, je bil cilj naše raziskave oceniti stopnjo povezanosti med izbranimi kazalniki kakovosti življenja (QoL) ter kliničnimi in slikovnimi kazalniki srčnega statusa v kontekstu zaznave poslabšanja QoL teh bolnikov.

Ključne besede:

antineoplastični agensi, kardiotskičnost, ventrikularna funkcija - levi, ventrikularna funkcija - desni, kakovost življenja, magnetno-resonančno slikanje, video, ehokardiografija, limfomi, Hodgkinova bolezen, neoplazme dojke

Metode: V kohortni klinični študiji v Hamburgu smo od avgusta 2017 do oktobra 2020 59 bolnikom z rakom, starim 18-80 let, pred kemoterapijo in več kontrolnimi pregledi, napravili oceno QoL z vprašalnikom EQ-5D in SF-36, hitro z deformacijo miokarda kodirano (fast-SENC) magnetnoresonančno slikanje srca (CMR), konvencionalno CMR, ultrazvočni pregled srca ter klinični pregled z določitvijo biomarkerjev. Podatke smo analizirali z analizo preživetja. Upad za več kot 5 % v vrednosti posameznega opazovanega kazalnika QoL je bil izbran kot opazovani dogodek. Razdelitev bolnikov v skupine je bila definirana glede na pojav kardiotskičnosti po njeni klinični definiciji, postavitve indikacije za zdravljenje z zdravili za zaščito srčne mišice ter na osnovi poslabšanja vrednosti posameznega opazovanega slikovnega kazalnika za več kot 5 % ob zadnjem kontrolnem pregledu v primerjavi z njegovo vrednostjo pred pričetkom kemoterapije.

Rezultati: Med kliničnimi kazalniki srčnega statusa je postavitve indikacije za zdravljenje z zdravili za zaščito srčne mišice pokazala statistično dobro povezanost s kazalniki QoL (EQ-5D $p = 0,028$; SF-36 telesna komponenta $p = 0,016$; SF-36 mentalna komponenta $p = 0,012$). Med slikovnimi kazalniki je bila MyoHealth ocena segmentne krčljivosti miokarda edina, ki je pokazala konsistentno dobro povezanost s kazalniki QoL (EQ-5D $p = 0,005$; SF-36 telesna komponenta $p = 0,056$; SF-36 mentalna komponenta $p = 0,002$).

Zaključek: Uveljavljeni fast-SENC kazalniki CMR so se pokazali za sposobne izpostaviti bolnike z zmanjšano QoL, ki potrebujejo pogostejšo/optimalnejšo obravnavo.

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1 INTRODUCTION

In the past 20 years, systemic cancer therapy has advanced considerably, lowering mortality and increasing life expectancy. With a substantially increased proportion of cancer survivors treated with chemotherapy, long term consequences of systemic chemotherapeutics have become a very important factor in the context of public health. A very prominent one among those is cardiovascular dysfunction due to cardiotoxic effects of chemotherapeutic regimes (1). Moreover, it is important to recognize that cancer patient quality of life (QoL) is also influenced by cardiovascular health (2), whose management is an important part of personalized patient management, which has been shown to improve survival and QoL in cancer patients (3), and has expanded to form its own clinical sub-field of cardio-oncology.

Chemotherapy drugs such as anthracyclines, taxanes, targeted biological therapies (trastuzumab, etc.), and drug combinations, with or without concomitant radiation therapy, have been shown to cause cardiotoxicity leading to heart failure (4, 5). In patients receiving anthracycline therapy, the incidence of chemotherapy-induced cardiotoxicity is approximately 30%, and can surpass many malignancies as the leading cause of mortality (6).

In the context of patient QoL, the clinical status as observed by the clinician is not reliable. It has been shown that attending physicians often underestimate chemotherapy-related symptom severity and frequency, with low sensitivity and specificity for detecting side effects of chemotherapy with or without concomitant radiation therapy, resulting in less than optimal treatment course decisions regarding chemotherapy continuation, halting, or dose alteration, as well as worse patient QoL (7).

It has also been shown that regular patient self-evaluation and reporting of QoL status can significantly improve physical and mental QoL metrics, reduce emergency room admittance, and even extend mean survival in patients with solid tumors by as much as 5 months, without increasing the cost in health resources (8).

Cardiac magnetic resonance (CMR) strain testing (strain-encoded, harmonic phase analysis) has been shown to detect cardiotoxicity before systemic changes occur. CMR strain has been shown to detect abnormal myocardial function in cancer patients treated with high-dose anthracycline chemotherapy despite normal systolic function by traditional metrics, namely traditional CMR and echocardiographic (ECHO) left ventricular ejection fraction (LVEF) (9).

With the aim of improving personalized treatment of patients on chemotherapy, the study's objective was to assess the degree of association between selected QoL indicators and both clinical and imaging cardiac status indicators when detecting deterioration in these patients' QoL.

2 METHODS

2.1 Study design

This study was part of the PREFECT research project (ClinicalTrials.gov identifier NCT03543228) (10), and was designed as a prospective cohort clinical study, performed in its entirety at the Katholisches Marienkrankenhaus GmbH.

2.2 Study population

In the period between August 2017 and July 2019, 63 patients were screened for their consent to study participation. The inclusion criteria were: age 18 to 80 years, any gender, in the case of women the absence of pregnancy, no contraindications for magnetic resonance imaging, breast cancer, non-Hodgkin's or Hodgkin's lymphoma, no history of prior chemotherapy or renal failure, a glomerular filtration rate of higher than 30ml/kg/m², and an indication to undergo chemotherapy for cancer treatment with or without concomitant radiation therapy. Those who agreed to participate, having provided written informed consent, were subsequently enrolled in the study.

2.3 Data collection procedure

Anti-cancer medications were prescribed at the attending oncologist's discretion, as per current European Society for Medical Oncology clinical practice guidelines (11). Patients with breast cancer were treated with epirubicin and cyclophosphamide every 3 weeks for a total of 4 cycles, followed by 12 weekly cycles of paclitaxel (EC-P); a few patients received dose-dense EC-P. Patients with HER2+ breast cancer were treated with trastuzumab and radiation therapy. Patients with non-Hodgkin's lymphoma were treated with cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP), while patients with Hodgkin's lymphoma were treated with a combination therapy including anthracyclines with or without radiation therapy.

Subjects were evaluated at baseline, 3-months, 6-months and 1-year follow-ups, and additionally as needed in between designated follow-up time points, using fast strain-encoded (fast-SENC) CMR, conventional CMR, and ECHO. They also had blood drawn for routine biochemical testing, including cardiac biomarker evaluation (troponin, brain natriuretic peptide, N-terminal pro b-type natriuretic peptide). At same time points as the above mentioned tests, all subjects were evaluated at the study location, with appropriate guidance, using EQ-5D and SF-36 QoL questionnaires.

2.4 Data collection instruments

2.4.1 QoL status measurement instruments

EQ-5D is a questionnaire-based tool for patient self-reported generic QoL measurement, developed and maintained by

the EuroQol Research Foundation. It combines a measure with five preference-based questions, and a visual analog scale (VAS). The five questions each describe one generic QoL aspect: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with two possible responses (absence of problems, presence of problems) in each. The responses were converted into index and utility scores anchored at 0 for death and 1 for perfect health. The VAS provides a measure of perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status) (12, 13). For the purpose of our study, we observed changes in the VAS score. The questionnaire has been in regular use in the clinical setting in the Germanophone world since 1998, after its German translation was validated (14). A newer version of the questionnaire, the EQ-5D-5L, providing 5 possible responses ranging from the worst possible health status to the best possible health status, was thereupon validated on the German population in 2014 (15). In our study, we used the original 2-level version, whose VAS component is the same as in the 5-level version.

SF-36 is a 36-item questionnaire-based tool for patient self-reported health-related QoL measurement, developed and maintained by the RAND Corporation. It has eight basic scores, describing different aspects of health-related QoL: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Each score is calculated (with weighting) from several preference-based questions with possible responses ranging from the worst possible health status to the best possible health status in either 2, 3, 5, or 6 increments, depending on the question. From the noted basic scores, two combined scores are derived: a physical health component score and a mental health component score. SF-36 also includes a single combined overview score, also derived from the eight basic scores, describing perceived change in patient's health status over the past year. Calculating each of the noted basic and combined scores gives a score ranging from 0 to 100. Higher scores indicate a better health status, and a mean score of 50 has been articulated as a normative value for all scores (16, 17). For the purpose of our study, we observed changes in the physical and mental component scores. The questionnaire has been in regular use in the clinical setting in the Germanophone world since 1994, since its German translation was validated (18). It was validated again in 1999 on a larger population of 6964 survey participants, resulting in a description of an updated German normative population sample (18).

2.4.2 Cardiac status measurement instruments

All traditional CMR and fast-SENC CMR measurements were performed with electrocardiogram triggering on the R-wave on a 1.5 Tesla Achieva magnetic resonance imaging

scanner, Philips Medical Systems International BV. Each patient received a comprehensive baseline CMR exam before initiating chemotherapy, which included steady-state free precession with global calculations (LVEF, volumes, mass), strain-encoded CMR, fast-SENC CMR, T1 and T2-weighted mapping, and adenosine perfusion stress testing. Conventional CMR acquisitions, including T1 and T2-weighted mapping images and strain-encoded CMR, were analyzed using the CVI 42 software package, Circle Cardiovascular Imaging, as per the manufacturer's training and recommendations. Fast-SENC CMR circumferential and longitudinal left ventricle and right ventricle strain were calculated and analyzed using the MyoStrain 5.0 software package Myocardial Solutions, Inc., as per the manufacturer's training and recommendations, to provide a validated, standardized left ventricle and right ventricle end-systolic segmental and global longitudinal and circumferential strain metrics (19).

ECHO LVEF was measured by the Simpson's method from biplane planes from the 2-chamber and 4-chamber views according to the manufacturer's training and recommendations. ECHO global longitudinal strain (GLS) was measured using speckle tracking algorithms incorporated into the Affiniti 50 G ultrasound machine, Philips Medical Systems International BV, according to manufacturer training and recommendations.

All laboratory analyses were performed as per standard operating procedures at the study institution's laboratories as well as an outsourced laboratory, Hämatologisch-Onkologische Praxis Altona.

2.5 Data analysis

2.5.1 QoL status indicators

An event was deemed to have occurred if a drop of more than 5% in each respective QoL status indicator score (EQ-5D score, SF-36 physical component score, SF-36 mental component score) was recorded as compared to its associated pre-chemotherapy value. The timepoint at the described event was thus recorded. If no event occurred, the last timepoint and QoL value was recorded. The observed outcome was the time (in days) from the baseline pre-chemotherapy examination to the target event.

In the analysis, three outcomes were observed: time to a drop of more than 5% in the EQ-5D score, time to a drop of more than 5% in the SF-36 physical component score, and time to a drop of more than 5% in the SF-36 mental component score.

2.5.2 Cardiac status indicators

The development of symptomatic heart failure, a significant reduction in LVEF, or cardiac biomarker indicators of myocardial injury were used to classify patients with subclinical cardiotoxicity and clinical

cardiotoxicity based on the American Society of Echocardiography Expert Consensus Position Paper, the European Society of Cardiology Position Paper, and the European Society for Medical Oncology clinical practice guidelines (11, 20, 21). Fast-SENC CMR was not used in categorizing cardiotoxicity status. Clinical cardiotoxicity was defined as an absolute change in LVEF from greater than 10% from baseline to below 53%, combined with heart failure symptoms or abnormal cardiac biomarker values (troponin, brain natriuretic peptide, or N-terminal pro b-type natriuretic peptide). Subclinical cardiotoxicity was defined as an asymptomatic patient with a greater than 15% decrease in LVEF that remains greater or equal to 53%, worsening in GLS of more than 15% from baseline, or abnormal cardiac biomarker values (troponin, brain natriuretic peptide, or N-terminal pro b-type natriuretic peptide). Patients with clinical cardiotoxicity and those with subclinical cardiotoxicity were combined into the “Cardiotoxicity” group, while the rest fell into the “No Cardiotoxicity” group.

The indication to initiate cardioprotective therapy was made at the discretion of the treating oncologist in consultation with a cardiologist. Establishment of the indication to initiate cardioprotective therapy was used to separate patients into the “Cardioprotection Indicated” and “No Cardioprotection Indicated” groups. Every patient who was indicated to receive cardioprotective therapy did so.

Whether or not the value of each respective cardiac imaging indicator (traditional CMR LVEF, traditional CMR GLS, ECHO LVEF, ECHO GLS, fast-SENC CMR LVEF, fast-SENC CMR standard parameters) worsened by more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value, was used to separate patients into the “Did Not Maintain Baseline” and “Maintained Baseline” groups for each respective cardiac imaging indicator. If a specific cardiac imaging indicator value worsened by more than 5%, the patient was grouped under “Did Not Maintain Baseline” for that specific cardiac imaging indicator. Otherwise, it was grouped under “Maintained Baseline” for that specific cardiac imaging indicator. An indicator’s worsening was indicated by a value decrease in LVEF measurements and fast-SENC CMR standard parameters, and a value increase in raw myocardial strain measurements (GLS).

2.5.3 Statistical analysis

Kaplan-Meier product limit statistic, along with the log-rank test, was used to assess the relationship between the observed QoL indicators and cardiac status indicators. The curves and statistics were graphed and calculated using Python 3.x, Python Software Foundation, with the lifelines 0.25.x package, <https://github.com/CamDavidsonPilon/lifelines>. P-values of <0.05 were considered statistically significant.

3 RESULTS

3.1 Observed patient group

All 63 patients who met the inclusion criteria agreed to participate and were enrolled into the study.

Of the 63 enrolled patients, 3 were excluded due to a change in therapy plan (non-chemotherapy cancer treatment), while another 1 patient was lost to follow-ups beyond the first visit. Results using the outcomes for the remaining 59 patients were subsequently used in all analyses.

Our population included 50 female and 9 male patients, with a median age of 51 years and mean of 53.9±14.5 years, respectively. Baseline QoL score values in the population were: EQ-5D median 75, mean 69.4±24.0; SF-36 physical component median 54.4, mean 51.1±8.6; SF-36 mental component median 44.8, mean 45.5±9.6.

3.2 Survival analyses

3.2.1 EQ-5D

Results of the association analysis for the observed EQ-5D outcomes are shown in Figures 1-3.

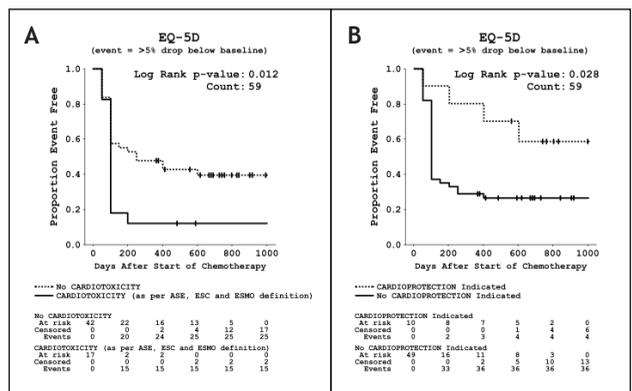


Figure 1. EQ-5D questionnaire events - (A) clinical definition of cardiotoxicity; (B) clinical indication for cardioprotective therapy initiation; Germany, single-center study, August 2017 through October 2020, chemotherapy for cancer treatment.

Clinical cardiotoxicity definition (Figure 1A) and the indication for cardioprotective therapy initiation (Figure 1B) both show statistically good association with EQ-5D scores.

Figure 2 shows that a worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in LVEF measurement values shows no association with EQ-5D scores, irrespective of the method used to obtain those values.

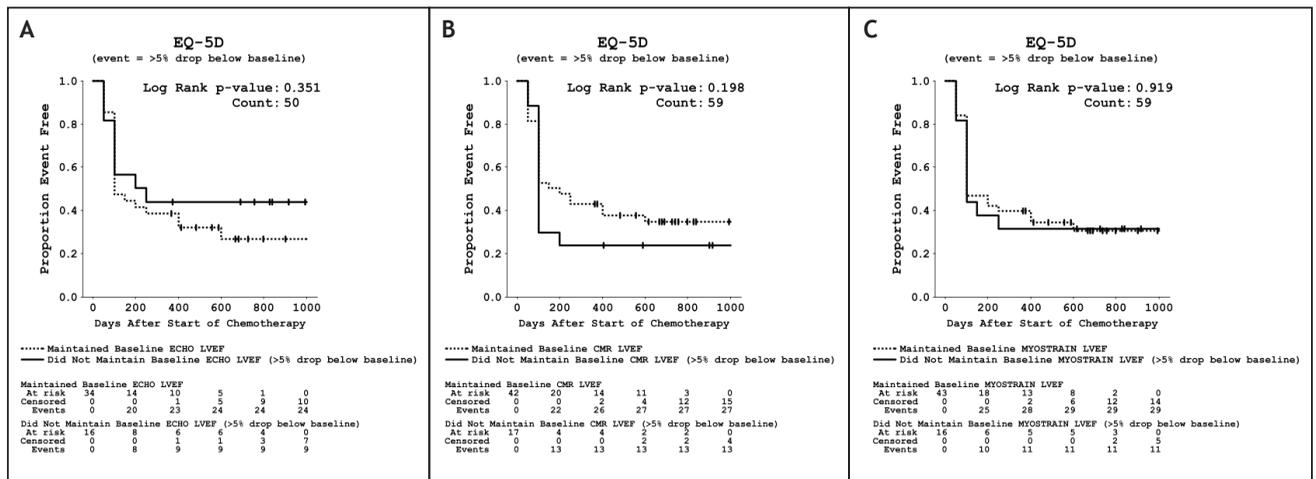


Figure 2. EQ-5D questionnaire events - traditional cardiac imaging modality metrics: (A) ECHO LVEF - echocardiographic left ventricular ejection fraction; (B) CMR LVEF - traditional cardiac magnetic resonance left ventricular ejection fraction; (C) MYOSTRAIN LVEF - fast strain-encoded cardiac magnetic resonance left ventricular ejection fraction; Germany, single-center study, August 2017 through October 2020, chemotherapy for cancer treatment.

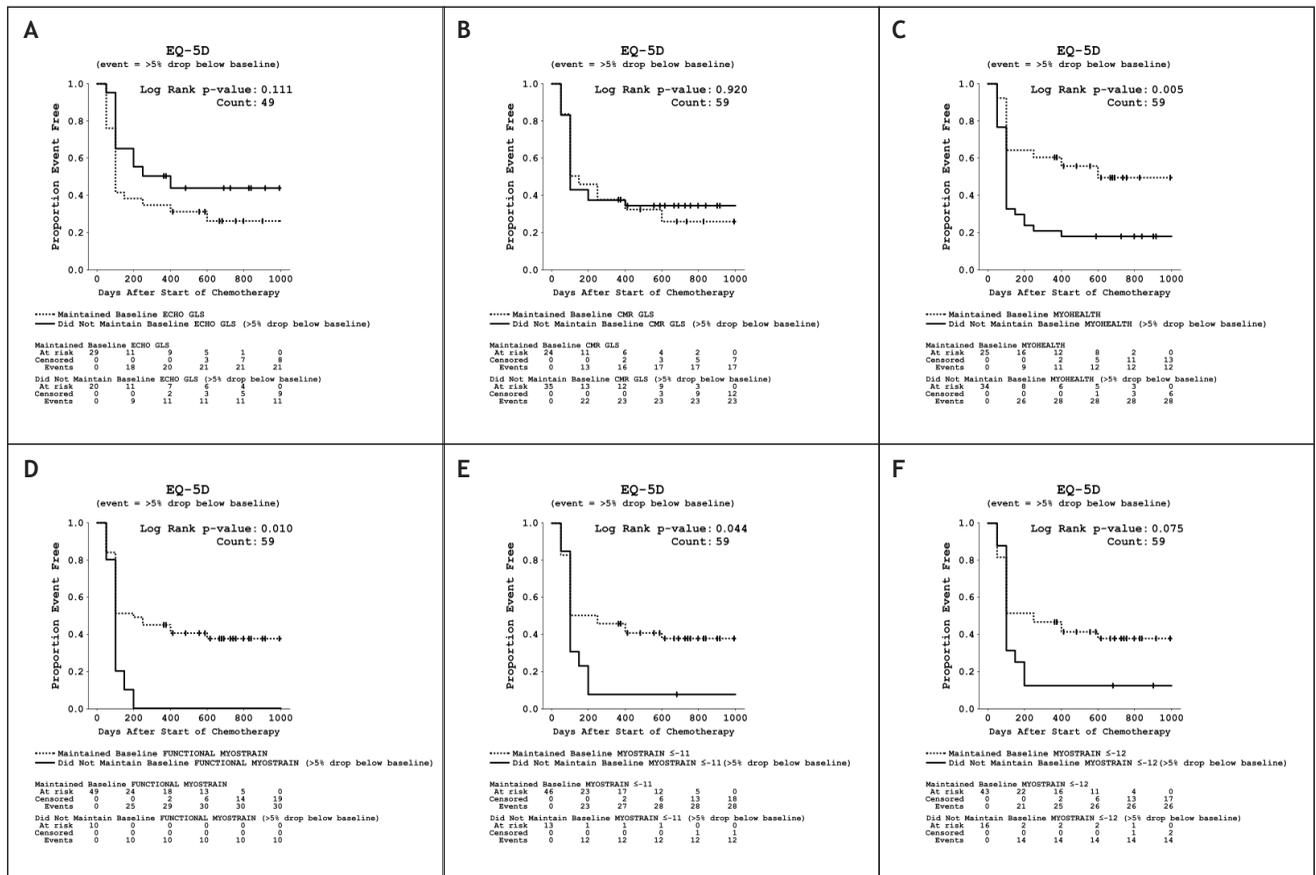


Figure 3. EQ-5D questionnaire events - myocardial strain imaging modality metrics: (A) ECHO GLS - echocardiographic global longitudinal strain; (B) CMR GLS - traditional cardiac magnetic resonance global longitudinal strain; (C) MYOHEALTH, (D) FUNCTIONAL MYOSTRAIN, (E) MYOSTRAIN ≤ 11 and (F) MYOSTRAIN ≤ 12 - percent of left ventricle longitudinal and circumferential fast strain-encoded cardiac magnetic resonance segments with normal, functional, $\leq 11\%$ or $\leq 12\%$ strain, respectively; Germany, single-center study, August 2017 through October 2020, chemotherapy for cancer treatment.

A worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in segmental myocardial strain scores all show either statistically good association (Figure 3C, D and E) or borderline association (Figure 3F) with EQ-5D scores, while there is no association between a worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in any of the observed global myocardial strain measurement values and EQ-5D scores, irrespective of the method used to obtain those values.

3.2.2 SF-36 physical component

Results of the association analysis for the observed SF-36 physical component outcomes are shown in Figures 4-6.

The clinical cardiotoxicity definition (Figure 4A) and the indication for cardioprotective therapy initiation (Figure 4B) both show a statistically good association with SF-36 physical component scores.

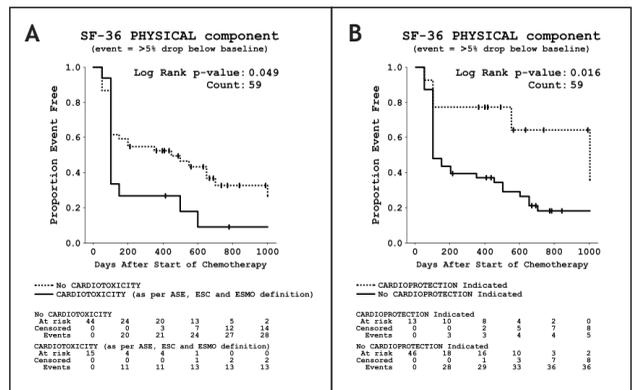


Figure 4. SF-36 physical component questionnaire events - (A) clinical definition of cardiotoxicity; (B) clinical indication for cardioprotective therapy initiation; Germany, single-center study, August 2017 through October 2020, chemotherapy for cancer treatment.

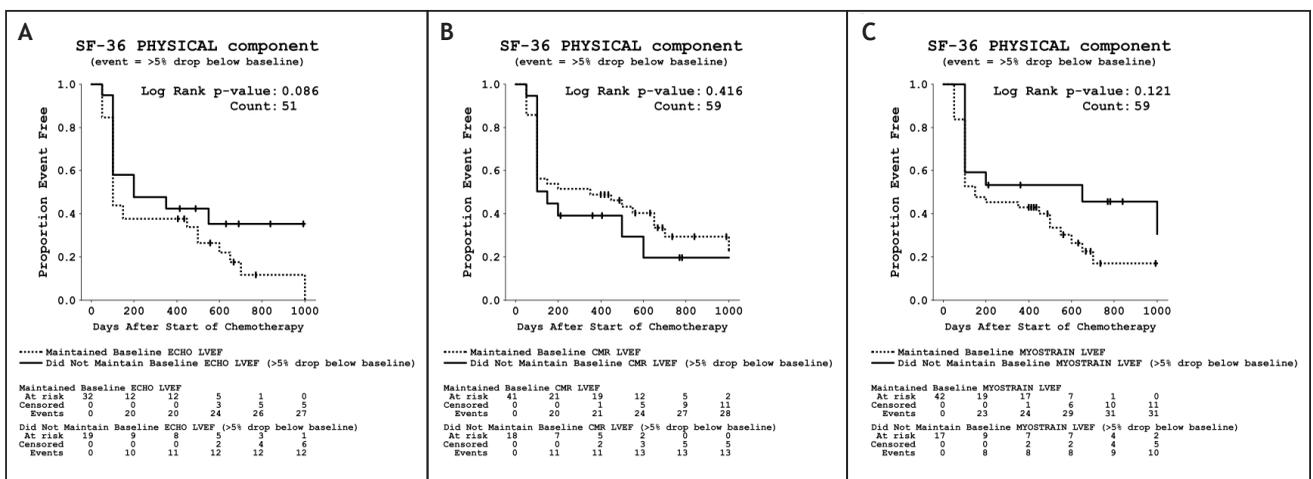


Figure 5. SF-36 physical component questionnaire events - traditional cardiac imaging modality metrics: (A) ECHO LVEF - echocardiographic left ventricular ejection fraction; (B) CMR LVEF - traditional cardiac magnetic resonance left ventricular ejection fraction; (C) MYOSTRAIN LVEF - fast strain-encoded cardiac magnetic resonance left ventricular ejection fraction; Germany, single-center study, August 2017 through October 2020, chemotherapy for cancer treatment.

Figure 5 shows that a worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in LVEF measurement values shows no association with SF-36 physical component scores, irrespective of the method used to obtain those values.

A worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in the MyoHealth score (Figure 6C) shows borderline association with SF-36 physical component scores, while a worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in all other observed myocardial strain indicators show no association with SF-36 physical component scores.

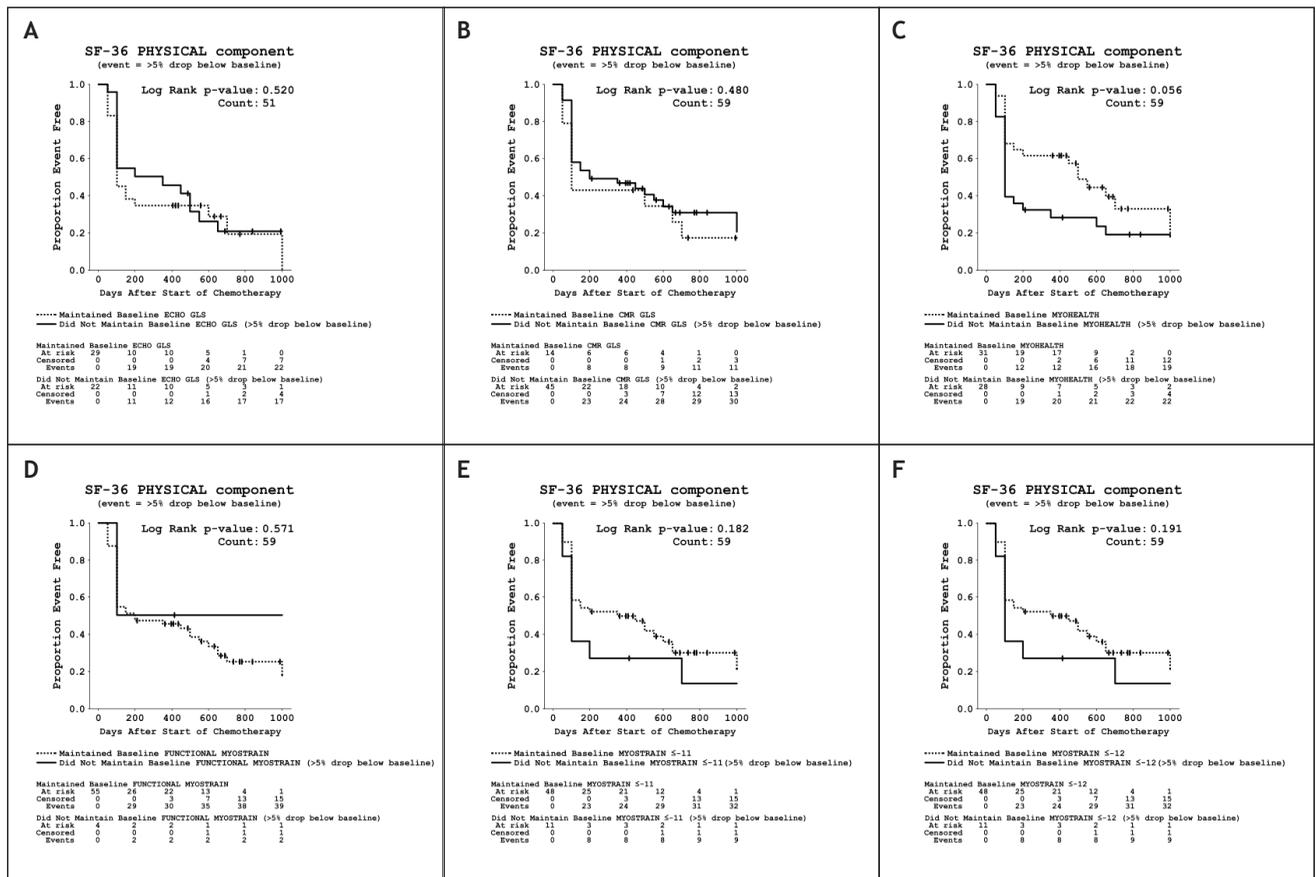


Figure 6. SF-36 physical component questionnaire events - myocardial strain imaging modality metrics: (A) ECHO GLS - echocardiographic global longitudinal strain; (B) CMR GLS - traditional cardiac magnetic resonance global longitudinal strain; (C) MYOHEALTH, (D) FUNCTIONAL MYOSTRAIN, (E) MYOSTRAIN \leq -11 and (F) MYOSTRAIN \leq -12 - percent of left ventricle longitudinal and circumferential fast strain-encoded cardiac magnetic resonance segments with normal, functional, \leq -11% or \leq -12% strain, respectively; Germany, single-center study, August 2017 through October 2020, chemotherapy for cancer treatment.

3.2.3 SF-36 mental component

Results of the association analysis for the observed SF-36 mental component outcomes are shown in Figures 7-9.

The indication for cardioprotective therapy initiation (Figure 7B) shows a statistically good association with SF-36 mental component scores, while the clinical cardiotoxicity definition (Figure 7A) shows borderline association with SF-36 mental component scores.

Figure 8 shows that a worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in LVEF measurement values shows no association with SF-36 mental component scores, irrespective of the method used to obtain those values.

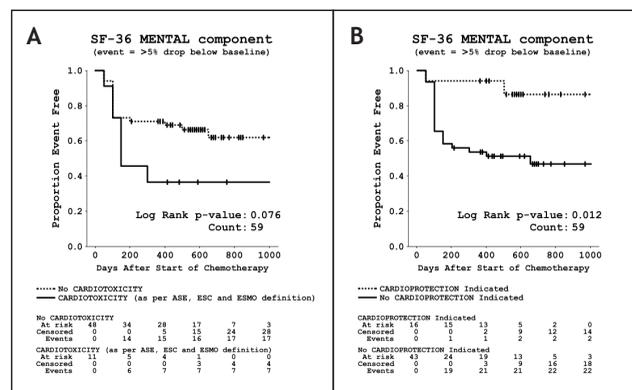


Figure 7. SF-36 mental component questionnaire events - (A) clinical definition of cardiotoxicity; (B) clinical indication for cardioprotective therapy initiation; Germany, single-center study, August 2017 through October 2020, chemotherapy for cancer treatment.

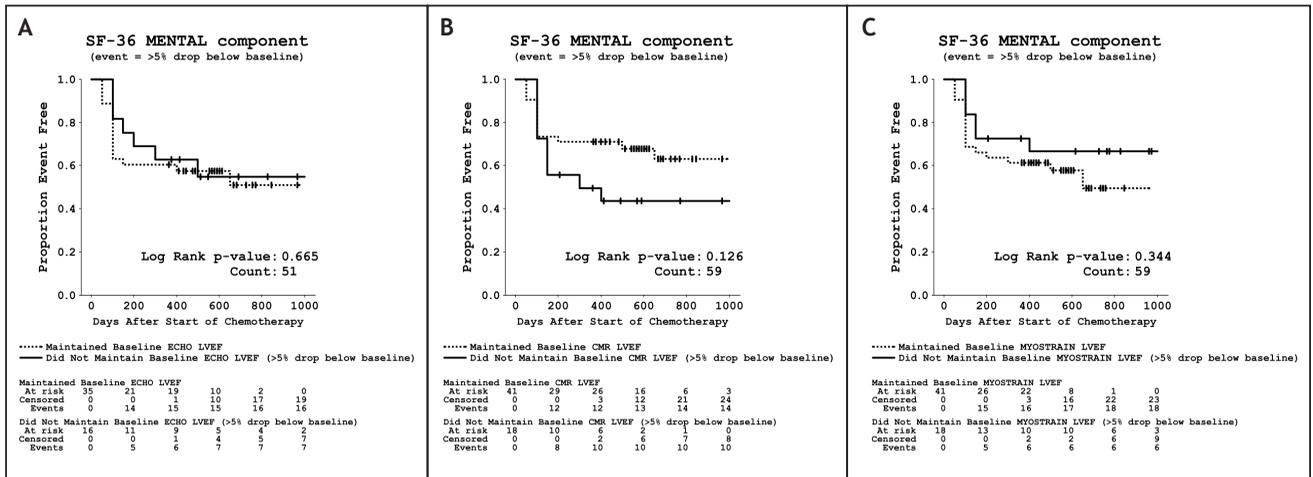


Figure 8. SF-36 mental component questionnaire events - traditional cardiac imaging modality metrics: (A) ECHO LVEF - echocardiographic left ventricular ejection fraction; (B) CMR LVEF - traditional cardiac magnetic resonance left ventricular ejection fraction; (C) MYOSTRAIN LVEF - fast strain-encoded cardiac magnetic resonance left ventricular ejection fraction; Germany, single-center study, August 2017 through October 2020, chemotherapy for cancer treatment.

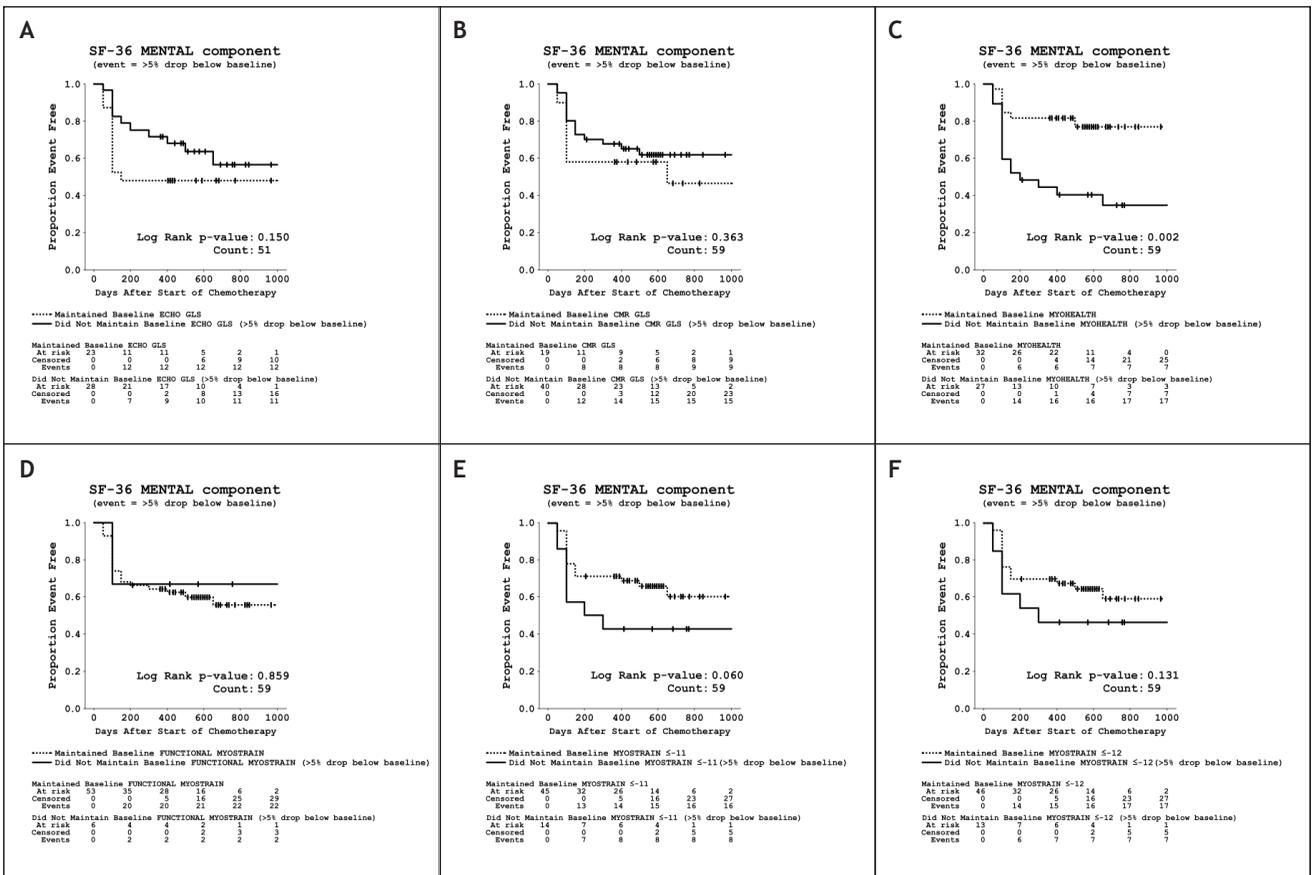


Figure 9. SF-36 mental component questionnaire events - myocardial strain imaging modality metrics: (A) ECHO GLS - echocardiographic global longitudinal strain; (B) CMR GLS - traditional cardiac magnetic resonance global longitudinal strain; (C) MYOHEALTH, (D) FUNCTIONAL MYOSTRAIN, (E) MYOSTRAIN ≤ 11 and (F) MYOSTRAIN ≤ 12 - percent of left ventricle longitudinal and circumferential fast strain-encoded cardiac magnetic resonance segments with normal, functional, $\leq 11\%$ or $\leq 12\%$ strain, respectively; Germany, single-center study, August 2017 through October 2020, chemotherapy for cancer treatment.

A worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in the MyoHealth score (Figure 9C) shows a statistically good association with SF-36 mental component scores, a worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in the percent of MyoStrain segments with contraction values of $\leq 11\%$ (Figure 9E) shows a borderline association with SF-36 mental component scores, while a worsening of more than 5% in the last follow-up compared to the corresponding pre-chemotherapy baseline value in all other observed myocardial strain indicators show no association with SF-36 mental component scores.

4 DISCUSSION

The differentiation in EQ-5D, SF-36 physical component and SF-36 mental component, observed in MyoHealth and Functional MyoStrain, successfully highlights the injury occurring from chemotherapy, which manifests in reduced QoL. Moreover, across each of the QoL metrics, MyoHealth was the single imaging parameter that consistently demonstrated the best delineation. Since MyoHealth correctly identified several events, the validity of associated statistical analyses, which showed that QoL results are best delineated by injury based on MyoStrain, is reinforced, suggesting that early identification of subclinical cardiotoxicity using fast-SENC CMR, with associated cardioprotection, may be able to impact QoL. Studies investigating QoL in cancer patients, more so cardiac patients in general, are numerous, both in the local (8, 22-24) and worldwide setting, as are those that investigate ECHO and traditional CMR measurements in relation to patient QoL. Comparison with similar studies to ours however is practically impossible due to the fact that fast-SENC CMR, as confirmed by the manufacturer, has never been analyzed in respect to patient QoL in any clinical scenario, including oncology. The only study done with fast-SENC CMR in vague relation to QoL was an economic evaluation of fast-SENC CMR in the diagnosis and management of early heart failure by Schneider and Stojanovic, published in 2019 (25).

Our study is limited by a few factors. The most important one is that the findings could be confounded by the impact of chemotherapy, cardioprotective medications, radiation therapy, comorbidities, age, and human psychology on perceived QoL. Chemotherapy and cardioprotective medications are known to have side effects that patients can perceive as reducing physical or mental conditions and therefore can impact EQ-5D, SF-36 physical component, and SF-36 mental component calculations. Radiation therapy is known to have a negative effect on regional myocardial performance, which is especially important in patients with breast cancer (26). Patients with a more

extensive array of comorbidities are much more likely to receive cardioprotection, which is bound to positively affect their QoL status both through the actual as well as placebo effects of cardioprotective medication, as opposed to their not cardioprotected counterparts. Lastly, age is also an important confounder in patient QoL self-estimation. To get around the noted limitations, multivariate models would need to be developed. Due to the small sample size however, this was not possible. The next limitation was the effect of differing patient-perceived QoL starting points at the baseline on observed data. The starting baseline QoL status after a confirmed diagnosis of cancer was bound to be higher in younger patients and those with fewer or no prior comorbidities, compared to older ones and those with more significant concomitant diseases. In our study, this was merited by observing the relative drop in QoL status, and thus the noted observation does not affect our conclusions. Finally, the log-rank test may not have been the best test choice in all cases, but we considered it good enough to roughly estimate the statistical significance of the differences.

On the other hand, our study also has some important strengths. The primary one is the fact that it is the first to investigate fast-SENC CMR in respect to patient QoL in any clinical scenario, both within and without the field of cardio-oncology. Also, using the Kaplan-Meier product limit statistic as the analysis tool, while not standard for this type of study, gives our results an additional time component, adding deeper insight into our observed population.

Our findings contribute in a meaningful way to both the cardio-oncology and public health fields. Fast-SENC CMR could, in addition to its original intended use for early cardiotoxicity detection and prediction, give regular follow-up imaging examinations an additional screening and diagnostic quality, both if used alongside questionnaire-based QoL analysis tools or without. In this context, fast-SENC CMR would serve as an indicator of the effect of anti-cancer therapy on the cardiovascular component of a patient's QoL, not influenced by other unwanted side effects of cancer treatment and elements from personal life that can influence various dedicated QoL tool scores. This would give the clinician valuable objective insight into this very important component of the overall patient QoL, which, if managed early with cardioprotective therapy, could greatly aid in quality personalized management of cancer patients, resulting in higher survival rates (3), better quality adjusted life years, and a lower burden on the healthcare system.

Numerous questions remain unanswered within the general topic our study. Firstly, a study on a larger patient population is merited. Furthermore, based on our findings, higher-risk patients could benefit from cardioprotective therapy that is instigated preemptively, even before subclinical changes in cardiac function can be

detected. In light of this, it could be beneficial to expand upon the scope of the research project this study is a part of by performing a randomized controlled trial on a select high-risk patient-group that could potentially benefit from initiation of cardioprotective therapy at the very beginning of their chemotherapy regimen. Moreover, for determining the optimal type, combination and regimen of cardioprotective therapy in cancer patients in general, another randomized controlled trial using fast-SENC CMR to follow patients' cardiac status would also be extremely beneficial, especially in the context of alleviating the public health burden imposed by the cardiotoxicity of chemotherapy and radiation therapy.

5 CONCLUSIONS

Established fast-SENC CMR scores including MyoHealth and Functional MyoStrain delineated patients who were predisposed to reduced QoL. The importance of appropriately classifying patients at risk of developing cardiotoxicity before and during cancer treatment has valuable potential clinical implications of highlighting patients who need to be monitored more frequently and managed more optimally.

CONFLICTS OF INTEREST

Henning Steen, Arne Kristian Schwarz, Sebastian Kelle, Grigorios Korosoglou and Daniel Lenihan hold a consulting position at and/or are in research collaboration with Myocardial Solutions, Inc. Other authors declare that no conflicts of interest exist.

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ETHICAL APPROVAL

The study was registered at ClinicalTrials.gov on 1 June 2018. The ethical approval was received from the ethical review board of the Hamburg Medical Association KdöR. The study complied with the Declaration of Helsinki, World Medical Association.

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