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Using heat maps to assess the multidimensional association of comorbidities with survival in older cancer patients treated with chemotherapy☆

Jae Jin Lee [a], Jongphil Kim [b,c], Marina Sehovic [a], Lu Chen [b], Martine Extermann [a,c,*]

[a] Senior Adult Oncology Program, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA
[b] Department of Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, USA
[c] Department of Oncology Sciences, University of South Florida, Tampa, Florida, USA

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ABSTRACT

Objective: To date, most comorbidity studies have analyzed either a subgroup of frequent diseases, or used summary instruments such as the Charlson score or the Cumulative Illness Rating Scale-Geriatric (CIRS-G). Yet, comorbidity is a multidimensional construct and impacts function, treatment tolerance, and survival. We assessed how heat maps can unveil specific patterns of comorbidities associated with overall survival (OS) in older cancer patients treated with chemotherapy.
Material and Methods: We reviewed four trials that prospectively evaluated comorbidities using CIRS-G. Eligible patients were 65 years or older and had solid tumors with 30 or more patients per tumor site. Heat maps were constructed based on CIRS-G scores and correlated with OS.
Results: Among 818 patients accrued, 399 were eligible: Median follow-up was 53.4 months and median OS was 19.6 months (95% CI: 16.5–24.2). In the univariate model for OS, patients with a severe CIRS-G score in 6 organ categories (3–4 in heart, hematopoietic, respiratory, and musculoskeletal-integument and 2–4 in upper GI and liver) had statistically worse OS than those with lower scores. According to a total risk score (TRS) based on hazard ratios for OS, OS of the low risk group ($N = 309$, $TRS < 2$) was significantly higher (24.3 m vs. 10.8 m, $HR = 2.05$, 95% CI: 1.58–2.66). TRS was a predictor for OS independently from stage, primary site, prior chemotherapy, ECOG performance status, and IADL ($HR = 1.94$, 95% CI: 1.47–2.57).
Conclusions: High TRS was a predictor of poor survival. Comorbidity heat maps appear promising to identify diseases most affecting the OS of older cancer patients.

1. Introduction

In 2015, in the United States, more than 50% of cancers occurred in people aged 65 and older [1]. Analyzing characteristics of these patients is very important in an aging society and increasingly older cancer patients.

Comorbidity increases with aging and cancer patients aged 70 and older have three or more comorbidities on average [2]. Comorbidity has been reported to affect the survival of cancer patients [3–6], and treatment-related toxicities [7–10]. Furthermore, comorbidity and its potential for related complications, or frailty interfere with physicians' treatment decisions for older cancer patients in poorly defined ways [11]. Comorbidity in the elderly should be considered as a factor when determining cancer therapy. Therefore, it is very important to define more precisely the role of comorbidity in older cancer patients.

Comorbidity is by essence a multidimensional construct, with highly variable physiopathologies and impact on function [2], treatment tolerance [12], cancer behavior [13–15], and survival [3–6,16] in cancer patients. The Cumulative Illness Rating Scale-Geriatric (CIRS-G) consists of fourteen organ categories including cardiac, vascular, respiratory disease, and so on and 5 levels of severity within each comorbid category [17]. It reflects the variety and complexity of the comorbidities. However, most comorbidity studies have analyzed either a subgroup of frequent diseases, or instruments summarizing the comorbidity burden, such as the Charlson score or CIRS-G. Although validated, these instruments usually rely on one end-point or expert consensus to build a severity rating. One can reasonably hypothesize that the subset of comorbidities that would most influence survival could be different from those that influence most physical function, or toxicity from treatment.

In order to further our understanding of comorbidity in cancer patients, we tested an analytic approach used in other multidimensional

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* Corresponding author at: Senior Adult Oncology Program, H. Lee Moffitt Cancer Center and Research Institute, 12902 USF Magnolia Dr, 33612 Tampa, FL, USA.
E-mail address: martine.extermann@moffitt.org (M. Extermann).

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problems such as gene expression or epigenetics, namely a heat map approach. Heat maps allow a two-dimension visualization of complex variables, helping distinguish how they cluster by outcome, synchronously with a visualization of their overall frequency and level of severity (or overexpression). They may also help visualize how sets of data associate with each other (e.g. comorbidities within patients). Heat maps are a supple way of displaying associations generated by a wide range of statistical methods. Although stricto sensu the same results could be expressed by data output tables, the length and complexity of these tables prevents an intuitive grasp of those results. In this article, we apply this approach to the correlation of comorbidity and survival in a large cohort of patients.

2. Materials and Methods

This is a retrospective study to assess the association of comorbidity, modeled with heat maps, with overall survival in a population of older cancer patients treated with chemotherapy. We reviewed four clinical trials that prospectively evaluated comorbidities using CIRS-G in our institution (H. Lee Moffitt Cancer Center) (Table 1). Eligible patients were 65 years or older and had solid tumors for which the number of patients by primary site was 30 or more. Among 818 patients accrued from July 2003 to June 2013, 399 were eligible: 90 with breast cancer, 77 with head and neck cancer, 71 with lung cancer, 66 with pancreatobiliary cancer, 53 with prostate and bladder cancer, and 42 with colorectal cancer. The reasons for exclusions were as below: 182 patients were treated in other locations than Moffitt Cancer Center, 99 were not evaluable for the original trials' end-points, 60 had hematologic malignancies, 48 had other solid tumors, 28 were less than 65 years old, and two had incomplete CIRS-G. All data were collected from the clinical trials databases, electronic records of Moffitt Cancer Center, and Total Cancer Care (TCC) Database.

Comorbidity was assessed by the CIRS-G which includes 14 organ categories with 5 levels of severity of comorbidities (score 0–4) [17,18]. The five summary scores are as follows: total number of categories endorsed, total score, ratio of total score/number of endorsed categories (severity index) and number of categories at level 3 and 4 for a given patient in CIRS-G. The 14 organ categories are as follows: Heart; Vascular; Hematopoietic; Respiratory; Eyes, ears, nose, throat & larynx; Upper GI; Lower GI; Liver; Renal; Genitourinary; Musculoskeletal/Integument; Neurological; Endocrine/Metabolic and Breast; and Psychiatric illness. We reviewed the 14 organ categories and 5 CIRS-G scores of the CIRS-G of our patients.

In addition, we reviewed patients' demographics, histology, year of diagnosis, cancer stage, prior and current cancer treatments, MAX2 index [12,19], and functional status (ECOG performance status (PS)) and Lawton's 9-item Instrumental Activities of Daily Living (IADL) scale [20] at study baseline. The MAX2 index ranks the average toxicity of a chemotherapy regimen based on the most frequent reported severe toxicities. Lawton's 9-item IADL is scored from 9 to 29 points (3 levels per item and 2 points for medications), 29 being best function.

Heat maps were created to visualize the comorbidity distributions using the following steps: 1) Each patient was attributed a line; 2) organ systems were attributed columns, and the heat color was based on each organ's CIRS-G severity rating, from blue (0) to red (4); and 3) the comorbidity types and levels of expression were grouped according to their relationship with overall survival, according to the statistical analysis described below.

This study was approved by the Institutional Review Board of the University of South Florida.

Table 2
Patients characteristics. Low-risk and high-risk mortality groups are defined on the basis of the comorbidity total risk score we constructed from our heat map analysis (see text for details).

Characteristics	All (N = 399)	TRS low risk (N = 309)	TRS high risk (N = 90)	p value
Age (y) median, range	74 (65–92)	74 (65–91)	74 (65–92)	0.27
Gender n (%)				0.027
Male	203 (50.9)	148 (47.9)	55 (61.1)	
Female	196 (49.1)	161 (52.1)	35 (38.9)	
ECOG PS n (%)				0.33
0	177 (44.4)	143 (46.3)	34 (37.8)	
1	157 (39.4)	116 (37.5)	41 (45.6)	
2	55 (13.8)	41 (13.3)	14 (15.6)	
3	10 (2.5)	9 (2.9)	1 (1.1)	
IADL median (range)	27 (12–29)	27 (12–29)	27 (15–29)	0.0503
Primary tumor site n (%)				<0.0001
Breast	90 (22.6)	81 (26.2)	9 (10.0)	
Head & neck	77 (19.3)	66 (21.4)	11 (12.2)	
Lung	71 (17.8)	37 (12.0)	34 (37.8)	
Pancreas, biliary	66 (16.5)	57 (18.5)	9 (10.0)	
Prostate, bladder	53 (13.3)	36 (11.7)	17 (18.9)	
Colon, rectum	42 (10.5)	32 (10.4)	10 (11.1)	
Stage[a] n (%)				0.13
I	16 (4.0)	15 (4.9)	1 (1.1)	
II	48 (12.1)	41 (13.3)	7 (7.8)	
III	78 (19.6)	56 (18.2)	22 (24.4)	
IV	256 (64.3)	196 (63.6)	60 (66.7)	
MAX2 index, median, range	0.13 (0.03–0.36)	0.13 (0.03–0.36)	0.12 (0.04–0.35)	0.15
Current chemotherapy n (%)				
Cisplatin-containing	54 (13.5)	44 (14.2)	10 (11.1)	0.45
Combined (≥3)	54 (13.5)	50 (16.2)	4 (4.4)	0.004
Prior therapy n (%)				
Chemotherapy	131 (32.8)	106 (34.3)	25 (27.8)	0.25
Surgery	248 (62.2)	191 (61.8)	57 (63.3)	0.79
Radiotherapy	94 (23.6)	79 (25.6)	15 (16.7)	0.08

[a] For one head & neck patient stage was not available. IADL = Instrumental Activities of Daily Living.

3. Statistics

Patients' clinical and demographical characteristics were summarized using descriptive statistics: frequency and proportion for categorical measures and mean, standard deviation, median, and range for continuous measures. Overall survival (OS) was measured from the date of initiation of treatment to date of death or last follow-up date. The association of comorbidity with categorical and continuous outcome was evaluated by the Chi-square test and the Kruskal-Wallis test. The survival function was estimated by the Kaplan–Meier method, and the difference between the functions was assessed by the log-rank test. The Cox proportional hazards regression model was used to assess the association with OS. The impact of comorbidity on OS was evaluated, and the risk score was developed based on the hazard ratio and significance; a risk score of 1 was given to those who had CIRS-G categories with p-value of <0.1 and hazard ratio of 1 to 2, and a score of 2 was assigned to those with a

Table 1
Trials used in the present project. Patients retained needed to be age 65 and older, have survival data available, and have a tumor type with 30 or more patients analyzable.

Trial	Cancer types	Treatment	Sites	# patients	Characteristics	# patients retained in project
Extermann et al. [10]	All except leukemia	Chemotherapy	Moffitt + community practices	518	Age 70 and older	207
Extermann et al. [31]	H&N	Chemoradiation	Moffitt	50	Age 65 and older	50
Raj et al. [32]	H&N	Chemotherapy	Moffitt	50	Adults	22
Extermann et al. [33]	All except leukemia	Chemotherapy	Moffitt	200	Age 70 and older	120

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