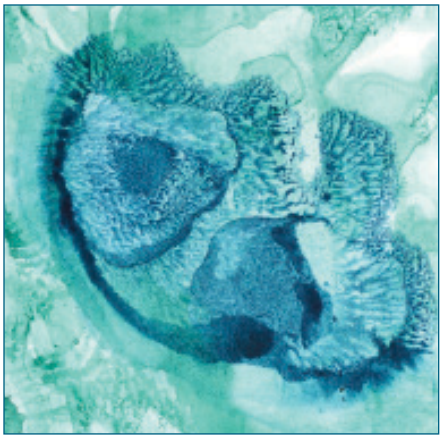

REVIEW

Role, Extent, and Impact of Comorbidity on Prognosis and Survival in Advanced Metastatic Melanoma: A Review

by FREDERICK N. BEBE, DrPH; SHASA HU, MD; TONY L. BROWN, MD, PhD; and ORIEN L. TULP, MD, PhD

Dr. Bebe is with the Kentucky State University College of Agriculture and Food Science and Sustainable Systems in Frankfort, Kentucky. Dr. Hu is with the Miller College of Medicine at the University of Miami in Miami, Florida. Drs. Brown and Tulp are with the University of Science, Arts and Technology Monserrat in the British West Indies and the College of Medicine and Graduate School in Denver, Colorado.

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ABSTRACT

Increased incidence of comorbidity in advanced metastatic melanoma (AMM) is emerging as an important factor in patient prognosis, treatment, and survival. This paper reviews the impact of comorbidities on the prognosis and survival outcomes of patients diagnosed with AMM. Our search initially yielded limited results. We then broadened our search to include breast, colorectal, and prostate cancer and covered malignancies in which screening (like melanoma) is associated with the detection of early-stage disease. Most studies showed that a higher prevalence of comorbidity was associated with more advanced cancer stage. Both treatment and survival of patients were influenced by age and the extent of comorbidity. Racial differences in survival were greatest for patients with no comorbidities and less evident at higher levels of comorbidity. Comorbid conditions showed differential effects for prognosis, treatment, and survival. Limited information in the literature demonstrates that more research is warranted with respect to comorbidities and AMM.

KEYWORDS: Comorbidity, prognosis, survival, advanced metastatic melanoma, race/ethnicity

Comorbidities are associated with disparities in treatment, clinical management, and health outcomes as well as increased health care costs in cases of metastatic disease. The prognosis, treatment, and survival of patients with advanced metastatic melanoma (AMM) depends on a number of factors, including age, stage, and the presence or absence of comorbidities.[1] Comorbidities can influence cancer detection, treatment, and progression, which in turn affect prognosis and long-term survival.[2,3] Comorbidity increases the odds of being diagnosed with distant metastasis and is associated with decreased survival.[4,5,6–12] Comorbidity elicits a higher risk of complications and lower performance status, decreased quality of life, and more life-threatening conditions.[11] However, despite the importance of considering comorbid diseases in the treatment and prognosis of melanoma, the association between melanoma and comorbidity has received little attention.[13,14]

Limited data have shown an association between comorbidities and a delay in melanoma diagnosis, more advanced stage, and less aggressive treatments, with comparable quality of life as that seen in the general public in localized metastatic melanoma patients.[11,15] Although survival is almost certain with early detection, this chance decreases with advanced age and significant comorbidities.[6] With the rapidly growing and aging population,[16] comorbidity could be an important factor in AMM prognosis, treatment, and survival, as is true in other cancers.

The incidence of melanoma has been steadily increasing at a rate of 1.4 percent per year over the past 10 years with increased rates among minorities and diagnosis being most frequent in people aged 55 years or older.[17] This signals an urgent need for further research regarding the impact of comorbidities on AMM outcome.

This paper reviews the available evidence on the impact of comorbidities on survival outcome of patients diagnosed with AMM. Compared with that on other malignancies, the existing literature on the subject of metastatic melanoma and comorbidity is limited. Therefore, selected studies were also drawn on the topics of breast, colorectal, and prostate cancers (Table 1), where (similarly to melanoma) screening is associated with detection of early-stage disease. A summary of the existing findings would help to guide future research in this area.

METHODS

Definition and measurement of comorbidity. Comorbidity is a concept that is often defined in relation to an index disease (i.e., the main condition or primary disease under

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CORRESPONDENCE: Frederick N. Bebe, DrPH; Email: frederick.bebe@kysu.edu

study0. It encompasses "medical conditions that exist at the time of diagnosis of the index disease or later but [which] are not a consequence of the index disease."[18] Feinstein[19] defined comorbidity as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study." This is distinguishable from the concept of multimorbidity, which is the "the coexistence of multiple chronic or acute diseases and medical conditions within one person without any reference to an index condition."[20]

Designation of the index or comorbid condition will depend on the research question, the disease episode, or the specialty of the attending physician.[21] In terms of AMM or other cancers, comorbidity relates to the "presence, nature, and severity of health-related conditions that exist alongside the cancer"[22] and is distinct in nature from multimorbidity, frailty (physiological state of increased vulnerability to stressors), performance or functional status (a measure of patient's ability to perform daily tasks), and patient factors. However, as Figure 1 shows, the interaction between comorbidity and related constructs or patient factors, frailty, and functional status might determine the outcome of AMM or other cancers, either independently or synergistically.

Comorbidity can be measured by counting the number of coexisting diseases diagnosed in a cancer patient or by using a comorbidity index that combines the number and severity of the comorbid diseases.[23] A number of indices have been validated, such as the Charleston Comorbidity Index (CCI), the Kaplan-Feinstein Index, the European Organization for Research and Treatment of Cancer Index (EORTC), the Adult Comorbidity Evaluation 27 (ACE-27), the Elixhauser Comorbidity Measure (23), and the C3 Index.[21] At this time, the most widely used index for comorbidities in cancer patients is the CCI index. The CCI score is the sum of weights of a patient's comorbid conditions based on 19 disease categories. The weights are derived from relative risk estimates obtained from a regression model. They are usually assigned from 1 to 6 points and then collapsed into categories of 0 points, 1 to 2 points, 3 to 4 points, and 5 or more points, respectively. The CCI has been previously validated as a prognostic marker of comorbidity for several index cancers.[24]

Literature search. The PubMed/MEDLINE database was used to search for articles on the impact of comorbidities on metastatic melanoma prognosis and survival. The following keywords were used: "comorbidity," "prognosis," "survival," "metastatic melanoma," and "race/ethnicity." Because very little has been published on comorbidity and melanoma to date, the search was broadened to include breast, colorectal, and prostate cancer, malignancies in which screening (like melanoma) is associated with the detection of early-stage disease. The search was not limited to any particular period. Overall, the search generated 1,135 articles; of these, 1,056 articles were eliminated and 79 abstracts were reviewed. Only 39 articles were subsequently retained for detailed reading and assessment, out of which 19 articles were selected. Notably, only two articles and three abstracts were found to be on metastatic melanoma prognosis, comorbidities, and survival (Figure 2). Articles that were neither selected nor reviewed as abstracts did not consider comorbidity. All articles were published between 1970 and 2016, including those described in Table 1.

RESULTS

Comorbidity and AMM prevalence, detection, and stage at diagnosis. A rapidly growing population and increasing longevity might result in increased prevalence of comorbidity; with this, the number of AMM patients with comorbidity might increase as well.[16,25,26] As reported in the SEER fact sheet for 2016, melanoma is most frequently diagnosed among people aged 55 years and older, with a median age of 63 years.[17] The incidence of melanoma has been steadily increasing at a rate of 1.4 percent per year for the past 10 years, and about 1,034,460 people were living with melanoma of the skin in the United States in 2013.[17] A recent report by Ma et al[27] showed a high prevalence of autoimmune comorbidity that increases over time in patients with newly diagnosed MM.

Patient comorbidity has a substantial impact on cancer stage at diagnosis.[4,11] In a cohort study conducted using Danish registry data of 23,476 melanoma patients, Grann et al[11] reported a higher prevalence of comorbidity associated with more advanced cancer stage. Similar results were obtained by Gonzales et al[5] using data from 32,074 patients from the Florida State Tumor Registry on colorectal, melanoma, breast, and prostate cancers. Comorbidity was associated with late-stage diagnosis in all four cancers, with the odds for late-stage melanoma being as high as 62 percent. The association of comorbidity and melanoma increasing the odds of distant metastasis could possibly give rise to a delay in melanoma diagnosis and less aggressive treatment.[11] However, the weight of the association varies by patient age, cancer type, specific comorbid disease, and overall comorbidity burden, as exemplified by the type of index measure used.[4,28,29]

Comorbidity and AMM prognosis, age, treatment, and survival. Increasing longevity and a rapidly aging population have made age and comorbidity increasingly important factors in clinical research and treatment.[30] The extent of comorbidities can impact AMM prognosis, treatment decisions, quality of life, and survival—especially in older patients. Comorbidities can increase the risk of complications, worsen comorbid diseases, and decrease functional status of metastatic melanoma patients receiving treatment.[11] In studying the interaction between melanoma diagnosis and comorbidity, Grann et al reported an interaction contrast (i.e., an "estimate of excess mortality beyond that expected from melanoma and comorbid diseases acting independently") that increased concurrently with the level of comorbidity, with the most severe group (≥4 points) having 101.1 deaths per 1,000 person-years.[11] The interaction contrast was also significant when stratified by melanoma stage at diagnosis, increasing concurrently with the level of comorbidity[11]—an indication of the level to which comorbidity could impact prognosis and survival. At the time of presentation, comorbidity was reported to be an independent predictor of decreased survival of high-risk and advanced melanoma patients, even when adjusted for stage at diagnosis, while a 22-percent risk of increased death was shown in multivariate analysis of melanoma patients with chronic lymphocytic leukemia as compared with those without comorbid disease.[31,32]

In colorectal and breast cancer patients, the strongest interaction between comorbidity and cancer affecting survival or mortality was observed in Danish patients with a CCI score of 4 points or above, especially in the first year of diagnosis.[33,34] In another European, population-based cancer registry study of breast cancer patients with comorbidities, comorbidity negatively affected prognosis independent of age, stage of disease, and treatment (hazard ratio: 103, p=0.0001 for one comorbid disease

TABLE 1. Summary of baseline patient disease characteristics (ITT population)

AUTHOR YEAR; COUNTRY	SAMPLE; STUDY PERIOD	CO-M ASSESSED	HYPOTHESIS/ OBJECTIVE	CO-M AFFECTED TREATMENT/ MORTALITY?	EFFECT ON SURVIVAL?	MAIN CONCLUSION(S)
Melanoma						
Grann et al[11] 2013; Denmark	Cohort of 23,4765 patients; 1897–2009	Yes (CCI) Interaction Contrast	Co-M negatively associated with survival; the more Co-M, the poorer the prognosis	Yes—mortality Possible—treatment	Possible (not assessed)	Co-M associated with advanced cancer stage, higher mortality
Schubert-Fritschle et al[15] 2013; Germany	Cohort of 664 patients; 2003–2004	Yes (EORTC score)	Chronic disease would affect QoL of MM patients	Not assessed	Not assessed	When compared with general population, localized MM does not worsen QoL; different Co-M have similar effects in MM
Peddi et al[31] 2012 (abstract); USA	Cohort of 444 patients; 2003–2006	ACE-27	Co-M would affect survival of patients with high-risk and advanced MM	Yes	Co-M significantly associated with stage and survival	Co-M at presentation were predictors of decreased survival, even following adjustment for age
Whitman et al[32] 2012 (abstract); USA	Cohort of 8,294 SEER patients; 1973–2008	Yes (single preexisting condition)	MM patients with preexisting lymphocytic leukemia more likely to die than MM patients without a secondary malignancy	Significant difference in mortality rates between groups, thus affecting survival		Primary and secondary MM with lymphocytic leukemia had 22% increased risk of death versus MM-only group
Ma et al[27] 2016 (abstract); USA	Cohort of 12,028 MarketScan patients; 2004–2014	Yes	Estimate prevalence of autoimmune Co-M and change over time	N/A	N/A	High comorbid disease burden associated with higher risk of autoimmune disorders; high prevalence of autoimmune Co-M; increases over time in new MM cases
Breast/colorectal/prostate cancer						
Gonzalez et al[5] 2001; USA	Cohort of 32,074 patients; 1994	Yes (CCI)	Co-M would be associated with late-stage diagnosis and higher mortality	Yes—mortality rates higher for each cancer	Possible (not assessed)	Co-M associated with late stage at diagnosis and higher overall mortality rates in all four cancers
Read et al[3] 2004; USA	Cohort of 11,558 patients;1995–2001	Yes (ACE-27)	Prognostic impact of Co-M would be greatest for cancer patients and their survival	Yes	Yes	Co-M had greatest impact on groups with highest survival rate and lease impact on those with lowest survival rate
Patnaik et al[35] 2011; USA	Cohort of 64,034 patients; 1992–2000	Yes (CCI)	Some Co-M will be more strongly associated with survival and mortality; associations may be modified by age	Yes; Co-M was associated with decreased overall survival and increased mortality		Stage I patients with Co-M had similar or poorer survival versus stage II patients without Co-M
Lund et al[37] 2008; Denmark	Cohort of 8,114 patients; 1995–2006	Yes (CCI)	Co-M disease may affect prostate cancer prognosis in newly diagnosed cases	Effect of Co-M on treatment and mortality not examined	Co-M had negative impact on survival	Co-M was a negative prognostic factor; survival occurred only in patients without survere Co-M
Land et al[9] 2012; Denmark	Cohort of 62, 591 patients; 1990–2008	Yes (CCI)	Assess effect of Co-M on mortality after early BC	yes	Yes	Survival did not improve with severe Co-M versus no Co-M; risk of mortality increased significantly with increased CCI score
Cronin-Fenton et al[7] 2007; Denmark	Cohort of 9,3000 BC patients; 1995–2005	Yes (CCI)	Examine influence of Co-M on survival and impact on relative mortality rates	Negative impact	Poor survival	Trend toward increased mortality and poor survival in BC patients with severe Co-M

Erichsen et al[33] 2013; Denmark	Cohort of 56,963 CRC and 271,670 non-CRC patients; 1995–2010	Yes (CCI)	Co-M would interact with CRC to increase mortality rate beyond that explained by CRC and Co-M acting independently	Yes	Not assessed	Co-M interacted with CRC to increase mortality beyond that explained by CRC and Co-M acting independently
Ording et al[34] 2013; Denmark	Cohort of 47,904 BC and 237,938 non-BC patients; 1994–2008	Yes (CCI)	Co-M would interact with BC to affect mortality, especially in the first year after BC diagnosis	Yes	Not assessed	Interaction between Co-M and BC affecting mortality was substantial, especially in patients with CCI score ≥ 4
Sarfati et al[22] 2014; New Zealand	Cohort of 269 Maori and 255 non-Maori patients; 2006–2008	Yes (C3 Index)	Investigate interrelationships between Co-M, treatment, and survival among stomach and liver cancer patients	Yes	Yes	Patients with Co-M were less likely to receive curative surgery and more likely to die versus those without Co-M
Hine et al[49] 2009; USA	Cohort of 496 colon cancer patients	Yes (ACE-27)	Access impact of Co-M and body mass index on survival and potential role in decreased survival of black patients with colon cancer	Yes	Yes	Co-M increased risk of death for black versus white patients, especially all-cause M and in those with early-stage tumors; Co-M not a contributing factor to decreased survival of black patients with colon cancer
Putt et al[47] 2009; USA	Cohort of 65- to 76-year-old prostate cancer patients (black=6,042 and white=47,458); 1999	Yes (ECM)	Investigate differential effect of Co-M on survival among elderly black and white patients newly diagnosed with prostate cancer	Yes	Yes	Greater Co-M was associated with decreased survival rates; racial disparities in survival decreased with increasing number of Co-M
Tammemagi et al[53] 2005; USA	Cohort of 906 BC patients (black=264 and white=642); 1985–1999	Yes (CCI)	Evaluate role of Co-M in racial survival disparity among BC patients	Yes	Yes	Black patients had more recurrence/progression, worse all-cause, and BC-specific survival; Co-M accounted for 40% of survival disparity
Freeman et al[46] 2004; USA	Cohort of 864 prostate cancer patients with diagnosis between 1986 and 1990	Yes (CCI)	Evaluate effect of Co-M on racial differences in surival among men with prostate cancer	Yes	Yes	Black patients had significantly greater mortality than from other causes, but differences disappeared as Co-M increased; absence of preexisting disease related to higher excess mortality risks for black patients
West et al[48] 1996; USA	Cohort of 1,196 BC patients; 1973–1986	Yes (CCI)	Significance of Co-M in understanding differences in survival between black and white women with BC	Yes	Yes	RRs for different levels of Co-M similar among black and white patients; thus, Co-M was an independent prognostic factor; CCI shown to predict survival of black and white women
Gomez et al[50] 2007; USA	Cohort of 41,901 CRC survivors; 1992–1996	Yes (CCI)	Study joint effects of SES, tumor characteristics, and SDFs on survival after CRC among and within racial/ethnic groups	Differential effects on treatment and survival		Co-M did not affect racial/ethnic differences in CRC cause-specific and all-cause mortality rates; survival differences between black and white patients remain unexplained

MM: metastatic melanoma; CCI: Charleston Comorbidity Index; Co-M: comorbidity; ERTC: European Organization for Research and Treatment of Cancer; ACE-27: Adult Comorbidity Evaluation 27; C3 Index: Cancer Care and Comorbidity Index; ECM: Elixhauser Comorbidity Measure; QoL: quality of life; BC: breast cancer; CRC: colorectal cancer; N/A: not applicable.

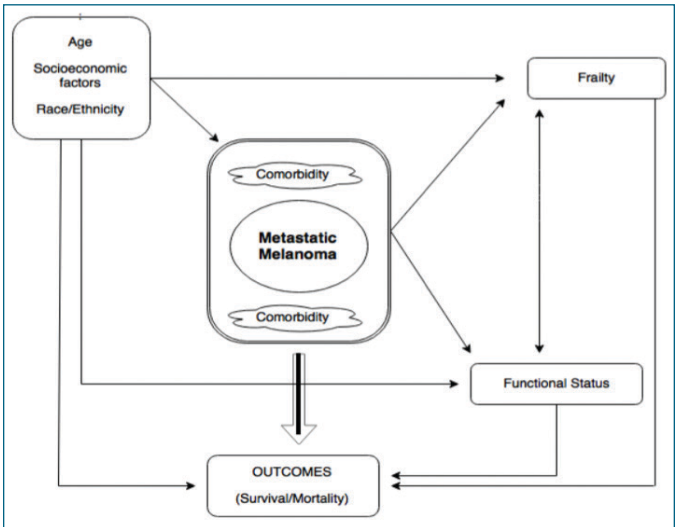

FIGURE 1. Interactions between comorbidity and age, socioeconomic factors, race/ethnicity, frailty, and functional status. Adapted from Sarfati D et al.[22]

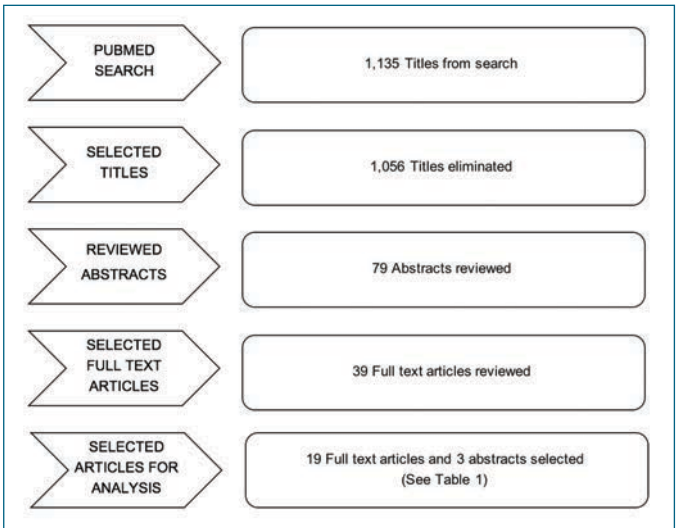

FIGURE 2. Article exclusion/inclusion flowchart.

and hazard ratio: 1.4, p=0.0001 for two or more comorbid diseases).[6] Patnaik et al[35] studied 13 comorbid conditions and reported each to be associated with decreased overall survival and increased mortality in breast cancer patients. Similarly, comorbidity had an independent prognostic effect on cancer survival, except in the case of tumors with very poor prognosis, on breast cancer-specific mortality as well as nonbreast-cancer mortality and on the survival of prostate cancer patients.[8,36,37] Likewise, in a Dutch study of patients with localized prostate cancer (1993–1995), comorbidity was also the most significant prognostic factor, especially for patients aged younger than 70 years.[38]

Treatment and consequent survival of AMM patients is influenced by age and extent of comorbidity. This can lead to less aggressive treatment or total exclusion from standard treatment and clinical trials, especially in individuals aged older than 70 years.[11,30] Even when alternative treatments are available, older colorectal cancer patients with comorbidities have been reported to be treated less aggressively than younger patients and to have worse survival than those without comorbidities.[39] Older patients with or without high comorbidity were also less likely to receive curative surgery and were more likely to die compared with younger patients or those without comorbidity.[40,41,42] In addition, the rate and frequency of administering adjuvant chemotherapy was found to decrease with increasing age and comorbidity.[36,39] Old age has been shown to be a significant and independent predictor of worse overall and disease-specific survival in breast cancer patients, as neither the severity of comorbidity nor differences in treatment between older and younger patients has a significant effect on survival.[42]

This disparity in treatment and subsequent survival is supported by the breast cancer study by Louwman et al,[6] in which the presence of comorbid conditions appeared to alter the therapeutic regimen independent of patient age and stage. The authors reported that the presence of comorbidity affected treatment in all age groups and was less extensive in older age groups with the effects being much smaller after the age of 70 years. In addition, patients with at least one serious coexisting disease received less radiotherapy and more systemic therapy compared with those without existing diseases. Further, when surgical procedures were examined, the proportion treated with surgery alone was lower and less extensive for patients with comorbidity but higher with systemic therapy.

In prostate cancer patients diagnosed with localized disease between1993 and 1995, comorbidity was the most significant prognostic factor for those younger than 70 years. However, the effects of comorbidity were strongest in younger men (≤60 years) and decreased with increasing age.[38]

Patients with one concomitant disease were twice as likely to die as those with none, while the presence of two concomitant diseases produced the largest negative effect on survival.[38] In a comparison of prostate cancer treatment and survival of men with and without comorbid diseases, Bradley et al[43] reported that men with multiple comorbid conditions were less likely to be treated than those without comorbidities. Fowler et al[44] reported highly significant associations between age and comorbidity (p<0.0001), as the age-adjusted risk of death was 5.7 times greater in men with severe comorbidity versus in those without comorbidity.

On the other hand, comorbidity might decrease survival because curative treatment is used less often in older patients. As a result, survival of patients older than 70 years was not significantly influenced by comorbidity.[38] The presence of comorbidity had little influence on treatment choice in patients with prostate cancer; instead, decision to treat was determined largely by patient age, tumor characteristics, and the experience of the urologist.[45]

Whether age could have an independent prognostic effect or have more influence on treatment chosen than comorbidity is yet to be studied in depth.[6] However, it is clear that comorbidity alone does not entirely explain why elderly patients undergo surgery less often or receive less treatment. Patient performance status, psychological condition, social and racial factors (Figure 1), and personal decisions might play a role.[36] Very few studies on these characteristics have been conducted to date on

AMM, so it remains to be seen whether or not similar effects apply to AMM patients.

Comorbidities and AMM survival among racial or ethnic groups. Although limited research in the area of melanoma has shown an association between comorbidities and a delay of melanoma diagnosis, more advanced stages of melanoma, and less aggressive treatments, survival is uncertain with increasing longevity and significant comorbidities.[11] The incidence of metastatic melanoma has been steadily increasing among minorities;[17] this creates an urgent need for research in the association between comorbidities and this condition. This association has received little attention and no studies have examined the racial differences in the relationship between comorbidity and AMM outcome.[13,14] The few examples from other malignancies would be helpful in illustrating this important relationship.

In a study on the effect of comorbidity on survival, Freeman et al[46] using chart (medical) review data of 864 prostate cancer patients demonstrated that racial differences in mortality were greatest for men with no comorbidities, with differences disappearing as comorbidity increased (1.75 [1.33–2.31] versus 0.90 [0.59–1.29]) for scores equal to 0 points and 5 points, respectively. Similar results were obtained by Putt et al[47] using a national cohort of more than 66,000 elderly black and white patients with localized prostate cancer. In this study, comorbidities were more prevalent among black patients than among white patients. Greater comorbidity was associated with decreasing survival rates for both sexes, but the effect among black patients was smaller than among white patients. Even after adjusting for age and socioeconomic status (SES), the association between increasing comorbidities and survival remained weaker for black patients than for white patients, although racial disparity in survival decreased with an increasing number of comorbidities. These differential effects of comorbidities on survival were also evident when examining different classes of comorbid conditions as well as relationships between comorbidity and the use of prostatectomy.[47]

On the contrary, a study by West et al[48] using the CCI index examined differences in survival in a cohort of 1,196 patients with breast cancer and found similar patterns of association with survival between black and white women. Comorbidity was neither a contributing factor to the decreased survival of black patients compared to white patients with colon cancer, nor did it have any impact on racial and ethnic differences in colorectal cancer survival among Medicare patients.[49,50] Similarly, Eley et al[51] found no association between comorbidity and breast cancer-specific survival among black and white patients with breast cancer.

DISCUSSION

Comorbidity has consistently been found to have an adverse impact on cancer survival. The magnitude of the association is variable depending on how comorbidity is measured, the measure of survival used, the cancer studied, and the population included.[22] This review demonstrates that comorbidity has a substantial but differential effect on stage, diagnosis, prognosis, treatment, and survival of patients with metastatic diseases; however, there is still much to be evaluated, especially with respect to AMM.

Comorbidity was reported to be an independent predictor of decreased survival of advanced melanoma patients.[31] The impact of comorbidity tends to increase with an increasing severity of comorbidity, as high levels of comorbidity are often associated with considerably higher risk of death compared with cases of no comorbidity.[22,52] Comorbidity was the most significant prognostic factor for those aged younger than 70 years; the effect was strongest in younger men (aged ≤60 years) and decreased with increasing age.[38]

A higher prevalence of comorbidity has been associated with more advanced cancer stage, giving rise to a delay in melanoma diagnosis.[4,11] Treatment and consequent survival of metastatic disease patients are influenced by age and extent of comorbidity, which might also lead to less aggressive treatment or total exclusion from standard treatment and clinical trials, especially in patients aged older than 70 years.[11,30] This results in a lowered chance of survival compared with patients without comorbidity, as the number of patients undergoing curative therapy decreased significantly with increasing age.[39,52]

Comorbidity might decrease survival because curative treatment is used less often in older patients, or treatments without curative intent might be used.[38,45] In a Dutch cancer registry study of prostate cancer patients newly diagnosed between 1995 and 2002 (N=6,340), Houterman et al[52] reported that increased levels of comorbidity led to less aggressive treatment that negatively affected the survival of older patients. The decision to treat was determined largely by patient age, tumor characteristics, disease stage, and experience of the urologist.[38,45]

As previously stated, whether age could have an independent prognostic effect[6] or have more influence on treatment chosen than comorbidity is yet to be studied in depth. Although comorbidity might be more important with the emergence of new treatment options, it is clear that comorbidity alone does not completely explain why elderly patients undergo surgery less often or receive less treatment. Patient performance status, socioeconomic and racial factors, and personal decisions might play a role.[36] Very few studies on these factors have been conducted regarding melanoma; it remains to be investigated whether similar effects occur in AMM patients.

Racial differences in survival or mortality were greatest for patients with no comorbidities, with differences disappearing as comorbidity increased. Comorbidities were more prevalent among black patients than among white patients. Greater comorbidity was associated with decreasing survival rates among black patients. Comorbidity was shown to be an independent predictor of overall and all-cause survival in black patients with breast cancer compared with white patients.[48] Even after adjusting for age and SES, the association between increasing comorbidities and survival remained weaker for black patients than for white patients, although racial disparity in survival decreased with an increasing number of comorbidities.[53] Most evidence suggests that the severity of common comorbidities is greater among minorities than among white people and that the greatest racial differences in survival are exhibited by patients with no comorbidities. These differential effects of comorbidities on survival were also evident when examining different classes of comorbid conditions.[47] In addition, reports of the impact of comorbidity on other malignancies have shown a racial disparity in the prognosis, treatment, and survival of patients with important implications for research in MM, as most studies regularly adjust for comorbidity in examining racial differences and few consider the interaction between comorbidity and race.[47]

On the contrary, comorbidity was neither a contributing factor for decreased survival of African-American Alabama hospital patients compared with Caucasian patients with colon

cancer, nor did it have any impact on racial and ethnic differences in colorectal cancer survival among Medicare patients.[49] Non-white individuals (especially black individuals) have been reported to develop more chronic diseases at earlier ages than white individuals.[54] This could give rise to survivor bias situations where only the more resilient minorities would live longer, thus representing a possible explanation for the lower effect of comorbidity on survival.[47] The fact that more black and Hispanic individuals are often diagnosed with more aggressive and advanced-stage cases of melanoma than white individuals could produce a minimal effect of comorbidity on treatment and overall survival. However, the impact of comorbidity tends to be greater for cancers with a better prognosis and for early-stage versus late-stage cancers.[41]

A number of reasons could explain why comorbidity impacts treatment decision and survival. Those with comorbidity receive less aggressive treatment than those without and experience higher levels of toxicity from cancer treatments, which might directly impact their survival possibilities. Secondly, the life expectancy of patients with comorbidity might reduce the motivation for these patients to receive more aggressive therapy with likely higher toxicity. Additionally, patients with higher comorbidity might decline treatment.[22] Some studies of the impact of comorbidity on treatment often report that patients with comorbidity who are treated have better survival outcomes than do those who are not. However, the decision to treat and the potential outcomes might be confounded by unmeasured factors, such as interaction with other drugs.[22]

Limitations. Studies that access the impact of comorbidity on prognosis, treatment, and survival outcomes of melanoma and other malignancies have several limitations. Most studies in this review are based on analyses of population-based cancer registry data linked with administrative data. Such data are generally adequate for determining the prevalence of comorbidity and survival outcomes but provide limited information on treatment delivery or patient tolerance for treatment regimens.[23] Administrative data, for example, have limited accuracy in some settings and results might not be generalized to other malignancies when single diseases are studied.[55] Studies relying on such databases might miss important comorbidities, underestimate their severity, or fail to address confounding factors such as smoking and other lifestyle aspects.[23] Also, the number of non-white individuals with AMM is substantially smaller than that of white individuals, so the ability to detect effects in black and Hispanic individuals is limited. Finally, this review only focused on AMM with examples from colorectal, breast, and prostate cancers; the generalizability of the findings to AMM or other cancers is unknown.

A further challenge in summarizing the effect of comorbidity on metastatic melanoma survival is the measurement of comorbidity. Comorbidity was measured in different ways in the studies under review, referring either to one specific disease or the aggregation of several diseases using an index (for example, CCI; Table 1), with little consideration of how specific conditions affected outcomes. It must also be noted that virtually none of the studies under review examined the impact of duration and/or the severity of comorbidity on cancer prognosis.[23]

Future studies and emphasis. A number of questions remain unanswered about the relationship between comorbidity and metastatic melanoma outcome (Figure 1). Thus, studies are needed that elucidate whether comorbidity in general or only specific diseases or disease combinations are associated with poorer survival. Studies with a more specific focus should be undertaken, including those that address the impact of an individual comorbidity on treatment. The importance of age and comorbid illness have received little attention and need to be integrated into treatment decisions and the determination of research outcomes.[30]

As reported by Sogaad et al[23] in their review of the impact of comorbidity in cancer survival, future studies on comorbidity and AMM should investigate how much of the impact of comorbidity could be attributable to comorbidity-related deaths or cancer-specific mortality and consider whether tumor biology or prognosis and survival in AMM is influenced by comorbidity. Given the dearth of research on racial and ethnic disparities in metastatic disease, it would be worthwhile to know if the negative impact of comorbidity is explained by racial or ethnic differences in SES or lifestyle factors. It would also be worthwhile to know if disparities in advanced melanoma survival among patients with comorbidity are related to severity and stage of the disease, physician recommendations, and patient preferences. In addition, useful future research would determine if comorbidity is associated with a higher risk of cancer treatment toxicity, given the limited participation of patients with comorbidity in randomized clinical trials. Lastly, in order to improve research on the impact of comorbidity on the survival of AMM patients, information on the level and severity of comorbidity must be obtained from different data sources (e.g., administrative data, chart review, and prescription and general practitioner records), using different measures of assessment. Such a strategy will increase the evidence from which effective treatment decisions could be made.

CONCLUSION

Importantly, this review is not a systematic review. In fact, many examples in the form of article cited come from other cancers, especially those for which screening is associated with the detection of early-stage disease. Comorbid conditions might have differential effects on survival after a diagnosis of AMM among black, Hispanic, and white patients. Racial disparities are most pronounced between black and white patients with no or few comorbidities and are less evident at higher levels of comorbidity.

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