TO THE EDITOR:

Associations between cohabitation status, treatment, and outcome in AML patients: a national population-based study

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Marital status is known to affect timely diagnosis, definitive treatment, and survival in solid cancers.[1] In contrast, inpatient management of hematological malignancies including acute leukemia has been suggested to reduce importance of adherence and home support when compared with other cancers.[2] However, few studies have investigated impact of these factors on treatment and outcome in patients with hematological diseases, and lack of individual-level socioeconomic and clinical data limits interpretation of previous findings.[1,3,4]

In some countries, as acute myeloid leukemia (AML) treatment and care have progressively shifted toward outpatient management,[5,6] identification of social, biological, or health care–related factors associated with health disparities may ensure adequate allocation of support and treatment to patients with inadequate social support networks, minimizing potential survival differences.[7] We therefore investigated how social support measured by cohabitation (ie, living with a partner) and marital status affects treatment intensity, treatment response, rate of hematopoietic stem-cell transplantation (HSCT), and survival in a large population-based AML cohort, using individualized socioeconomic and clinical data.

We identified 3495 patients with nonpromyelocytic AML diagnosed from 2000 to 2014 through the Danish National Acute Leukemia Registry.[8] We excluded patients age ≤25 years, thus increasing the likelihood of patients being old enough to engage in cohabitant relationships (supplemental Figure 1, available on the *Blood* Web site). Detailed methods are available in supplemental data.

We linked data using the civil person registration number (supplemental Figure 2).[9] Socioeconomic information was retrieved the year before AML diagnosis.[10] As social support indicator, we used cohabitation, defined as living with another adult person with age difference of <15 years vs living without a partner.

Second, analyses were repeated using marital status (married, never married, divorced, or widowed). Additional socioeconomic information included education level, household income, and occupation.[11] Clinical information included among others cytogenetic Medical Research Council risk profile,[12] AML type (de novo,

secondary, or therapy-related AML),[13] Eastern Cooperative Oncology Group performance status (PS), and non–leukemia-related comorbidity.[14]

Treatment intensity was described as selection for remission induction chemotherapy, clinical trial inclusion, and HSCT performance.[15] Treatment outcomes were complete remission (CR; after up to 2 cycles of induction chemotherapy)[16] and all-cause mortality. Patients were followed from date of diagnosis until death, emigration, or end of follow-up (18 February 2016).

By logistic regression, we calculated crude and adjusted odds ratios (aORs) for receiving intensive chemotherapy by cohabitation and marital status. In patients receiving intensive therapy, we assessed chance of CR, clinical trial inclusion,[17] and, in eligible patients, HSCT according to clinical guidelines (intermediate and adverse cytogenetic risk patients age ≤70 years achieving CR).[15] Survival, overall and in patients receiving intensive therapy only, was described using Kaplan-Meier curves and Cox proportional hazards regression (hazard ratios [HRs]). Analyses were stratified by age and sex.

The study population included 3243 patients (patients receiving intensive therapy, 50%; median age, 59 years). Socioeconomic and demographic characteristics varied by cohabitation status; however, leukemia characteristics did not differ between groups (supplemental Table 1).

Associations between cohabitation and treatment outcomes are listed in Table 1. Living alone was associated with a lower likelihood of receiving intensive therapy than cohabitating (37.2% vs 57.5%; aOR, 0.60; 95% CI, 0.46-0.77). However, among patients age <60 years, this difference diminished (94.5% vs 90.8%; aOR, 0.95; 95% CI, 0.46-1.95). The proportion of patients receiving less-intensive therapy over supportive care was comparable between patients living alone and cohabitating (14.0% vs 13.5%; age- and sex-adjusted relative risk, 1.03; 95% CI, 0.83-1.2). In patients receiving intensive therapy (n = 1623), PS, comorbidity burden, and disease characteristics were comparable between groups. Time from diagnosis to chemotherapy initiation (3.5 days; interquartile range, 1-7 days), chances of clinical trial

Table 1. Association between cohabitation status and allocation to intensive therapy and HSCT in first CR

Cohabitation status	Patients, outcomes, n (%)	OR* (95% CI)	aOR† (95% CI)	aOR†‡ (95% CI)
Intensive therapy				
All patients	3243			
Cohabitating	2056 (57.5)	1.0	1.0	1.0
Living alone	1187 (37.2)	0.44 (0.38-0.51)	0.58 (0.46-0.73)	0.60 (0.46-0.77)
Age <60 y				
Cohabitating	622 (94.5)	1.0	1.0	1.0
Living alone	251 (90.8)	0.57 (0.33-0.99)	0.66 (0.35-1.26)	0.95 (0.46-1.95)
Age ≥60 y				
Cohabitating	1434 (41.2)	1.0	1.0	1.0
Living alone	936 (22.8)	0.42 (0.35-0.50)	0.60 (0.46-0.78)	0.61 (0.46-0.81)
Trial inclusion				
Patients receiving intensive chemotherapy	1623			
Cohabitating	1182 (31.6)	1.0	1.0	1.0
Living alone	441 (28.6)	0.86 (0.68-1.10)	0.88 (0.68-1.12)	0.90 (0.70-1.17)
CR				
Patients receiving intensive chemotherapy	1623			
Cohabitating	1182 (70.6)	1.0	1.0	1.0
Living alone	441 (72.8)	1.11 (0.87-1.42)	1.06 (0.81-1.37)	1.06 (0.81-1.39)
HSCT in first CR				
HSCT candidates§	964			
Cohabitating	702 (19.0)	1.0	1.0	1.0
Living alone	262 (11.8)	0.57 (0.38-0.87)	0.46 (0.28-0.76)	0.47 (0.28-0.78)

CI, confidence interval; SES, socioeconomic status.

*Crude.

†Adjusted for age, sex, and clinical factors, including white blood cell count, cytogenetic risk group, World Health Organization performance status, type of leukemia (de novo, secondary, or therapy-related AML), and comorbidity.

‡Adjusted for SES, including income, educational level, and occupation.

§Patients excluded from analysis: not reaching CR, n = 2038; favorable cytogenetic risk group, n = 84; age >70 years, n = 157.

enrollment (31.6% vs 28.6%) and CR did not differ overall or within age groups. In contrast, in potential HSCT candidates, patients living alone were less likely to undergo HSCT than cohabitating patients (19.0% vs 11.8%; aOR, 0.47; 95% CI, 0.28-0.78).

We followed patients for a median of 183 days (interquartile range, 43-166 days). During the combined follow-up of 5710 years, 2794 deaths occurred. Patients living alone had lower survival (1 year: 29.2% vs 40.7%; 5 years: 9.5% vs 18.1%; supplemental Figure 3) compared with cohabitating patients. The overall all-cause mortality was increased in patients living alone (aHR, 1.20; 95% CI, 1.10-1.31). Stratifying by age, cohabitation only affected survival in older patients (aHR, 1.21; 95% CI, 1.09-1.33). Limited to patients receiving intensive therapy, any effect of cohabitation disappeared after adjustment for other socioeconomic factors (Table 2).

In general, similar results were found using marital status as exposure. A tendency toward worse outcome was observed in never-married patients (supplemental results; supplemental Tables 2 and 3). No differences were observed between men and women.

To our knowledge, the importance of cohabitation has not previously been examined in patients with AML. Our findings suggest that lower rates of remission induction therapy and lower rates of HSCT as postremission therapy are prominent contributors to the inferior survival observed both in patients living alone and in unmarried patients. Individual-level income,

education, and occupation did not explain the effect of cohabitation or marriage in older patients, supporting the hypothesis that cohabitation mediates its benefits through increased social support, rather than through better financial or material resources related to cohabitation.

Lower HSCT rates in patients with suboptimal insurance coverage have been reported previously.[18-20] However, disease-, treatment-, and individual-level socioeconomic information was not taken into account. Our results raise the important question of whether selection of cohabitating patients and married patients for intensive therapy and postremission HSCT is driven by physicians' bias regarding socioeconomic status or by well-informed patient-driven decisions. In AML, expedited treatment decisions are recommended to reduce the risk of clinical deterioration.[21,22] Spouse and/or first-degree relatives may be more likely to advocate for intensive therapies for a leukemic patient, whereas older patients living alone and patients without first-degree relatives may be more likely to opt out of chemotherapy and/or consolidating HSCT when presented with the dismal prognosis, likely adverse effects, and possible complications.

Advanced-stage presentation of cancers is a well-documented explanation for inferior outcome in unmarried patients with solid cancers.[3,23] We found, however, comparable disease characteristics in patients living alone and cohabitating patients, suggesting that delayed diagnosis cannot explain inferior survival in patients with

Table 2. Effect of cohabitation status on overall survival in all 3243 patients with AML and in 1623 receiving intensive, overall and by age

Cohabitation status	Patients, n (%)	HR* (95% CI)	aHR† (95% CI)	aHR†‡ (95% CI)	aHR†§ (95% CI)	aHR†‡§ (95% CI)
All patients						
Any age						
Cohabiting	2056 (63.4)	1.0	1.0	1.0	1.0	1.0
Living alone	1187 (36.6)	1.38 (1.29-1.50)	1.21 (1.11-1.31)	1.19 (1.10-1.30)	1.20 (1.11-1.31)	1.20 (1.10-1.31)
Age <60 y						
Cohabiting	622 (71.2)	1.0	1.0	1.0	1.0	1.0
Living alone	251 (28.8)	1.12 (0.94-1.35)	1.18 (0.99-1.42)	1.07 (0.89-1.29)	1.13 (0.94-1.36)	1.05 (0.87-1.27)
Age ≥60 y						
Cohabiting	1434 (53.7)	1.0	1.0	1.0	1.0	1.0
Living alone	936 (39.5)	1.38 (1.27-1.50)	1.19 (1.08-1.30)	1.20 (1.09-1.33)	1.19 (1.08-1.30)	1.21 (1.09-1.33)
Patients receiving intensive therapy						
Any age						
Cohabiting	1182 (72.8)	1.0	1.0	1.0	1.0	1.0
Living alone	441 (27.2)	1.05 (0.93-1.20)	1.09 (0.93-1.20)	1.06 (0.93-1.21)	1.11 (0.97-1.26)	1.08 (0.95-1.24)
Age <60 y						
Cohabiting	588 (72.1)	1.0	1.0	1.0	1.0	1.0
Living alone	228 (27.9)	1.06 (0.88-1.29)	1.12 (0.92-1.35)	1.04 (0.86-1.29)	1.07 (0.88-1.30)	1.01 (0.82-1.23)
Age ≥60 y						
Cohabiting	594 (73.6)	1.0	1.0	1.0	1.0	1.0
Living alone	213 (26.4)	1.08 (0.91-1.28)	1.08 (0.91-1.28)	1.11 (0.92-1.32)	1.13 (0.95-1.35)	1.16 (0.96-1.39)

Cox regression analysis.

*Crude.

†Adjusted for age and sex.

‡Adjusted for SES, including income, educational level, and occupation.

§Adjusted for clinical factors, including white blood cell count, cytogenetic risk group, World Health Organization performance status, type of leukemia (de novo, secondary, or therapy-related AML), and comorbidity.

AML living alone. Our findings suggest that social support is more important in older patients, whereas prior data from our group have shown that educational level is a greater determinant of treatment decisions in younger patients.[10]

Linkage of high-quality data allowed for a truly population-based design with virtually complete follow-up. Detailed individualized socioeconomic and clinical data enabled us to investigate how social support affects AML outcome. We lacked information on lifestyle-related factors; however, results were adjusted for lifestyle-related comorbidity and PS.

Several European and American countries offer universal health care. The Danish population has free access to universal health care, including diagnostic workup, treatment, and comprehensive follow-up. No cancer treatment takes place outside public hospitals. Our study settings are thus not directly referable to countries where income and insurance influence health care access, and the associations we found could be even stronger in less supportive social security systems.

In summary, cohabitation and marital status have substantial effect on treatment decisions and overall survival in patients with AML age ≥60 years. Patients living alone were less likely to receive remission induction chemotherapy or undergo post-remission HSCT, potentially leading to inferior outcomes. Our results suggest that social effects, rather than material resources, explain this association. Once a treatment decision was made (best supportive care, lower-intensity regimens vs intensive chemotherapy), cohabitation status did not affect survival. Attention toward reasons driving decision making in older patients living alone is important to reduce health disparities and improve survival.

Authorship

Contribution: L.S.G.Ø., J.M.N., M.N., and B.C.M. were responsible for conception and design and analyzed and interpreted data; L.S.G.Ø., J.M.N., C.S., M.T.S., C.W.M., and L.S.F. collected and assembled data; all authors were responsible for writing the manuscript and final approval of manuscript; and L.S.G.Ø. had full access to all study data and had final responsibility for the decision to submit for publication.

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Footnotes

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TO THE EDITOR:

Nonspecific inhibition of erythropoiesis by short hairpin RNAs

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RNA interference, including ectopic expression of short hairpin RNAs (shRNAs), provides a powerful approach to studying developmental pathways and genes of interest. We used this method to study Trim58, an E3 ubiquitin ligase that is highly expressed in late-stage erythroid precursors in which it facilitates degradation of the dynein molecular motor complex.[1] In a widely