

Impact of Comorbidities on Survival Among Patients with Chronic Myeloid Leukaemia Using the Charlson Comorbidity Index

Retrospective study from Basra, Iraq

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تأثير الأمراض المصاحبة على البقاء على قيد الحياة بين مرضى سرطان الدم النخاعي المزمن باستخدام معيار تشارلسون للاعتلال المشترك

دراسة استيعادية من البصرة، العراق

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ABSTRACT: Objectives: In chronic diseases, comorbidities are known to have a strong negative association with overall survival (OS). This study aimed to use the Charlson Comorbidity Index (CCI) to examine the effect of comorbidities on OS among patients with chronic myeloid leukaemia (CML) treated with tyrosine kinase inhibitors. **Methods:** This retrospective study was conducted between January 2006 and October 2016 and included 247 CML patients treated at the Basra Oncology & Haematology Centre, Basra, Iraq. Information from hospital records was used to calculate CCI scores and patients were divided into groups based on scores of 2–3 (CCI1 group) or ≥ 4 (CCI2 group). The OS was calculated using Kaplan-Meier curves. **Results:** There were 177 (71.7%) patients in the CCI1 group and 70 (28.3%) in the CCI2 group. Overall, patients in the CCI1 group were significantly younger compared to those in the CCI2 group (median age: 35 versus 60 years; $P < 0.001$); however, the gender distribution was similar in both groups (male-to-female ratio of 1:1.06 versus 1:1.18, respectively; $P = 0.683$). Diabetes mellitus was the most common comorbidity (17%), followed by hypertension (12%) and gastrointestinal diseases (6%). There were no significant differences in mortality between the groups (9.6% versus 8.6%; $P = 0.801$). In total, 69.6% of all deaths were related to CML progression rather than to the presence of comorbidities. **Conclusion:** No significant correlation was found between CCI score and OS among CML patients in Basra. However, larger long-term prospective studies are needed to evaluate associations with median age at diagnosis and disease severity and to develop region-specific prognostic scales.

Keywords: Comorbidity; Chronic Myeloid Leukemia; Mortality; Survival Analysis; Chronic Diseases; Iraq.

المخلص: الهدف: من المعروف أنه في الأمراض المزمنة يكون للأمراض المصاحبة ارتباط سلبي قوي مع البقاء على قيد الحياة بشكل عام. تهدف هذه الدراسة إلى استخدام معيار تشارلسون للاعتلال المشترك لفحص تأثير الأمراض المصاحبة على البقاء على قيد الحياة بشكل عام بين مرضى سرطان الدم النخاعي المزمن الذين عولجوا بمثبطات التيروسين كيناز. **الطريقة:** أجريت هذه الدراسة الاستيعادية بين يناير 2006 وأكتوبر 2016 وشملت 247 من مرضى سرطان الدم النخاعي المزمن والذين عولجوا في مركز البصرة للأورام وأمراض الدم، البصرة، العراق. تم استخدام المعلومات في سجلات المستشفى لاحتساب مجموع نقاط معيار تشارلسون للاعتلال المشترك وتم تقسيم المرضى إلى مجموعات على أساس مجموع النقاط: 2-3 (المجموعة الأولى) أو ≥ 4 (المجموعة الثانية). وتم احتساب معدل البقاء على قيد الحياة باستخدام منحنيات كابلان ماير. **النتائج:** كان هناك 177 (71.7%) مريضاً في المجموعة الأولى و 70 (28.3%) في المجموعة الثانية. وبشكل عام كان عمر مرضى المجموعة الأولى أصغر بكثير مقارنة بمرضى المجموعة الثانية (متوسط العمر: 35 مقابل 60 سنة؛ $P < 0.001$)، بينما كان التوزيع بين الجنسين متشابهاً في كلا المجموعتين (نسبة الذكور إلى الإناث من 1:1.06 مقابل 1:1.18، على التوالي؛ $P = 0.683$). كان داء السكري الاعتلال المشترك الأكثر شيوعاً (17%)، يليه ارتفاع ضغط الدم (12%) والأمراض المعوية المعوية (6%). لم تكن هناك فروقات ذات دلالة إحصائية في معدل الوفيات بين المجموعتين (9.6% مقابل 8.6%؛ $P = 0.801$). وفي المجمل كان ما نسبته 69.6% من جميع الوفيات مرتبطة بتطور سرطان الدم النخاعي المزمن وليس بسبب وجود الأمراض المصاحبة. **الخلاصة:** لم يتم العثور على علاقة ذات دلالة إحصائية بين مجموع نقاط معيار تشارلسون للاعتلال المشترك والبقاء على قيد الحياة بين مرضى سرطان الدم النخاعي المزمن في البصرة. ومع ذلك هناك حاجة إلى دراسات مستقبلية أوسع وطويلة الأجل لتقييم ارتباطات متوسط العمر عند التشخيص مع شدة المرض وتطوير مقاييس التنبؤ الخاصة بكل منطقة.

الكلمات المفتاحية: الاعتلال المشترك: سرطان الدم النخاعي المزمن؛ وفيات؛ تحليل البقاء على قيد الحياة؛ الأمراض المزمنة؛ العراق.

ADVANCES IN KNOWLEDGE

- The median age of patients with chronic myeloid leukaemia (CML) in Basra, Iraq, was lower compared to those reported in Western countries.
- The majority of deaths were attributable to disease progression, rather than the presence of comorbidities.

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- Larger prospective studies are needed to confirm the findings of the current study and to evaluate the potential role of comorbidity treatment on survival. Such data may help in the development of region-specific prognostic scales.

APPLICATION TO PATIENT CARE

- There is no decrease in overall survival due to the presence of comorbidities among chronic myeloid leukaemia patients in Basra, Iraq, and patients may present at a younger age in comparison to those in Western countries.

WORLDWIDE, CHRONIC MYELOID LEUKAEMIA (CML) accounts for approximately 15% of all types of leukaemia in adults.¹ Although there is paucity of epidemiological data, the incidence of CML is usually considered similar across the globe.^{2,3} Studies from North America and Europe have reported an age-adjusted incidence of 0.6–2 and 0.7–1 per 100,000 individuals, respectively.^{3,4} However, in Iraq, the age-standardised incidence of leukaemia has been reported as 3.9–4.3 per 100,000 individuals.^{5,6} The varying prevalence and mortality rates of CML may be due to differences in accessibility to treatment options; for example, the availability of tyrosine kinase inhibitors (TKIs) has significantly decreased annual CML-related mortality rates to <2–3%.^{2,7} Ironically, however, this decrease in mortality has increased the prevalence of CML worldwide.^{2,3,8}

Comorbidities are defined as distinct additional clinical conditions that either pre-exist or occur during the course of a primary disease.⁹ Comorbidities have a strong negative association with overall survival (OS) among patients with chronic diseases; for example, in cancer patients, comorbidities can affect the diagnosis, treatment and outcomes.¹⁰ Comorbidities can also increase the cost of treatment and decrease the patient's quality of life.¹¹ The presence of comorbidities has been shown to influence OS in chronic lymphocytic leukaemia (CLL).^{10,12} Similarly, comorbidities have also been reported to have a negative impact on OS among CML patients; however, there is no effect on treatment success with TKIs.^{13,14}

The impact of comorbidities on disease outcomes can be measured by a well-established and validated 20-item risk-scoring tool, the Charlson Comorbidity Index (CCI).^{15,16} This tool is based on the principle that age and the presence and severity of comorbidities increase the likelihood of mortality among patients who receive treatment for chronic illnesses. Scores for each item range from 1–6, with the maximum score given in the presence of a metastatic tumour or acquired immune deficiency syndrome; age is also considered a risk factor, with an additional point for each completed decade beyond 40 years.¹⁵

To the best of the authors' knowledge, the use of prognostic scales such as the CCI has not been adequately studied among CML patients in Iraq and other Middle Eastern countries. This study aimed to

evaluate the effect of comorbidities and age on OS among patients with CML treated with imatinib or other TKIs using the CCI.

Methods

This retrospective study was conducted between January 2006 and October 2016 at the Basra Oncology & Haematology Centre, Basra, Iraq. A total of 285 CML cases registered at the Basra Oncology & Haematology Centre during the study period were reviewed. Only CML patients treated with TKIs and who underwent regular follow-up were enrolled in the study (N = 247). Patients who discontinued treatment for over three months continuously (including pregnant women) and those who did not have regular follow-up visits during the study period were excluded at the time of screening.

The clinical and demographic information necessary to calculate CCI scores were extracted from the patients' hospital records, including age, gender, date of diagnosis, duration of treatment, outcome and cause of death. The medical records also included a detailed patient history and results of a physical examination in addition to the initial CCI score, an essential part of early assessment for every patient prior to receiving therapy. The overall CCI scores were calculated according to Table 1.¹⁵ Based on their scores, patients were divided into two groups; those with scores of 2–3 were assigned to the CCI1 group, while patients with higher scores of ≥ 4 were allocated to the CCI2 group.

In cases where patients had a history of past illnesses that fell within the CCI parameters (i.e. aortic aneurysms of ≥ 6 cm, dementia, chronic pulmonary disease or peptic ulcer disease), the previous diagnosis and management of the illness was reviewed with relevant specialists, if necessary. In order to evaluate the molecular response to TKI treatment, patients underwent regular *breakpoint cluster region-Abelson murine leukaemia* screening every six months using the GeneXpert[®] assay (Cepheid Inc., Sunnyvale, California, USA). In order to avoid bias, the analyst was blinded to the patient details.

The statistical analysis was conducted using Epi Info[™] software, Version 3.3 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA). The

cause of death was evaluated and recorded individually for each patient while the mortality rate was calculated for the overall study population. For the purposes of the study, OS was defined as the time between diagnosis and death, irrespective of the administration of TKIs. The OS probabilities were calculated using Kaplan-Meier curves. A *P* value of <0.05 was considered statistically significant.

This study was reviewed and approved by the Medicine Ethical Committee of Basra College of Medicine, Basra, Iraq (#569). All procedures and protocols involved in this study were conducted in accordance with the principles of the revised Declaration of Helsinki.

Table 1: Weighted scores for each item of the 20-item Charlson Comorbidity Index¹⁵

Item	Weighting
1. Age	Score of 1 for every decade over 40 years of age
2. History of myocardial infarct (not ECG changes alone)	Score of 1 per item
3. Congestive heart failure	
4. Peripheral vascular disease including aortic aneurysms of ≥6 cm	
5. Cerebrovascular disease (i.e. accident with mild or no residual impact or a transient ischaemic attack)	
6. Dementia	
7. Chronic pulmonary disease	
8. Connective tissue disease	
9. Peptic ulcer disease	
10. Mild liver disease without portal hypertension and including chronic hepatitis	
11. Diabetes without end-organ damage (excluded in patients on dietary control alone)	
12. Haemiplegia	Score of 2 per item
13. Moderate or severe renal disease	
14. Diabetes with end-organ damage (i.e. retinopathy, neuropathy, nephropathy or brittle diabetes)	
15. Tumour without metastasis (excluded if >5 years since diagnosis)	
16. Leukaemia (acute or chronic)	Score of 3
17. Lymphoma	
18. Moderate or severe liver disease	
19. Metastatic tumour	Score of 6 per item
20. Acquired immune deficiency syndrome	

ECG = electrocardiography.

Results

A total of 285 CML cases were registered at the Basra Oncology & Haematology Centre during the study period; of these, 247 (86.7%) patients treated with TKIs and followed-up regularly were included in the analysis. The median age of these patients was 43.5 years (range: 5–102 years old) and the male-to-female ratio was 1:1.09 [Table 2]. Based on their CCI scores, 177 (71.7%) patients were allocated to the CCI1 group (i.e. those with lower CCI scores) and 70 (28.3%) to the CCI2 group (i.e. those with higher CCI scores). Patients in the CCI1 group were considerably younger than those in the CCI2 group (median age: 35 versus 60 years; *P* <0.001). However, the gender distribution was similar in both groups (male-to-female ratio of 1:1.06 versus 1:1.18; *P* = 0.683) [Table 3].

The median duration of follow-up was 50 months (range: 2–198 months). The most common comorbidity was diabetes mellitus (17%), followed by hypertension (12%) and gastrointestinal disorders (6%). The least common comorbidities were hepatitis, neurological disorders and other cancers (1% each) [Figure 1]. Almost all (94%) of the patients were initially prescribed 400 mg of imatinib; however, 88 (38%) of which were later switched to 800 mg of nilotinib. In contrast,

Table 2: Age and gender distribution of patients with chronic myeloid leukaemia in Basra, Iraq (N = 247)

Age in years	n (%)			Cumulative percentage
	Male (n = 118)	Female (n = 129)	Total	
<10	2 (1.7)	2 (1.6)	4 (1.6)	1.6
10–19	8 (6.8)	6 (4.7)	14 (5.7)	7.3
20–29	18 (15.3)	15 (11.6)	33 (13.4)	20.6
30–39	24 (20.3)	29 (22.5)	53 (21.5)	42.1
40–49	20 (16.9)	25 (19.4)	45 (18.2)	60.3
50–59	29 (24.6)	27 (20.9)	56 (22.7)	83
≥60	17 (14.4)	25 (19.4)	42 (17)	100

Table 3: Age and gender distribution according to comorbidity groups of patients with chronic myeloid leukaemia in Basra, Iraq (N = 247)

Characteristic	Total	Group*		<i>P</i> value
		CCI1 (n = 177)	CCI2 (n = 70)	
Median age in years (range)	43.5 (5–102)	35 (5–59)	60 (37–102)	<0.001
Male-to-female ratio	1:1.09	1:1.06	1:1.18	0.683

CCI = Charlson Comorbidity Index.

*As assessed using the Charlson Comorbidity Index, with patients receiving scores of 2–3 or ≥4 assigned to the CCI1 and CCI2 groups, respectively.¹⁵

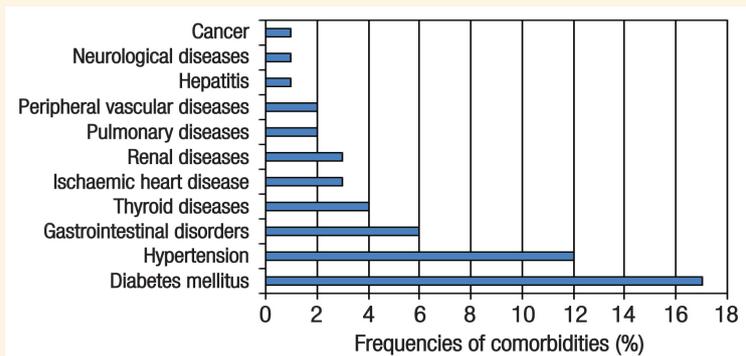


Figure 1: Frequency of comorbidities among patients with chronic myeloid leukaemia in Basra, Iraq (N = 247).

Table 4: Mortality rate according to comorbidity groups among patients with chronic myeloid leukaemia in Basra, Iraq (N = 247)

Group*	n (%)					
	Dead			Alive		
	Total	Male	Female	Total	Male	Female
CCI1 (n = 177)	17 (9.6)	9 (5.1)	8 (4.5)	160 (90.4)	77 (43.5)	83 (46.9)
CCI2 (n = 70)	6 (8.6)	3 (4.3)	3 (4.3)	64 (91.4)	29 (41.4)	35 (50)
Total	23 (9.3)	12 (4.9)	11 (4.5)	224 (90.7)	106 (42.9)	118 (47.8)

CCI = Charlson Comorbidity Index.

*As assessed using the Charlson Comorbidity Index, with patients receiving scores of 2–3 or ≥4 assigned to the CCI1 and CCI2 groups, respectively.¹⁵

15 patients who were initially administered nilotinib continued taking it throughout the study period. Overall, 55.7% of patients responded to treatment; however, 14.9% had suboptimal results and 29.4% failed to respond at all.

A total of 23 patients died during the study period, resulting in a mortality rate of 9.3%. The median age of those who died was 44 years, while the median age of those who survived was 43 years. Mortality rates were similar for patients of both genders and across both CCI1 and CCI2 groups [Table 4]. There was no significant difference in mortality according to the CCI score (9.6% versus 8.6%; $P = 0.801$). Of the 23 deaths, analysis showed that 69.6% were related to CML progression, rather than comorbidity burden. The remaining 30.4% of deaths were due to ischaemic heart disease (8.7%), other cancers (8.7%; including one case each of transitional cell carcinoma of the bladder and laryngeal cancer), renal failure (4.3%), a cerebrovascular-related accident (4.3%) and a war injury (4.3%). Figure 2 shows the Kaplan-Meier cumulative survival curve for the two groups across the follow-up period.

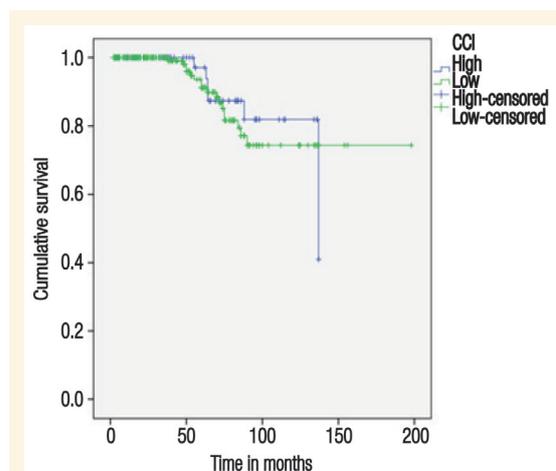


Figure 2: Kaplan-Meier survival curve showing cumulative survival according to comorbidity groups* among patients with chronic myeloid leukaemia in Basra, Iraq (N = 247).

CCI = Charlson Comorbidity Index.

*As assessed using the Charlson Comorbidity Index, with patients receiving scores of 2–3 or ≥4 assigned to the CCI1 and CCI2 groups, respectively.¹⁵

Discussion

The CCI tool assesses the presence and severity of various comorbidities as parameters in the prognostic analysis of chronic diseases and has been utilised successfully among patients with a variety of illnesses, including CML, CLL and myelodysplastic syndrome.^{10,12,13,15} Among CML patients, clinical studies have utilised the CCI to evaluate the effect of comorbidities on OS, event-free survival, remission rates, progression of the disease to accelerated phase or blast crisis, onset of complications, compliance to treatment and all-cause or cancer-specific mortality rates.^{13,14,17–21} In CML, most previous studies have evaluated the association between CCI and survival outcomes in patients being treated with imatinib; however, Breccia *et al.* reported its use among those treated with other TKIs (i.e. dasatinib).^{13,14,17–21}

As the availability of TKIs has markedly decreased mortality rates among CML patients, appropriate information regarding risk factors or poor prognostic markers can help in the individualisation of therapy.⁷ As such, findings from the present study may be helpful as a basis for the development of a modified risk assessment system for patients with CML in Iraq. Use of an appropriate prognostic scale can help in the appropriate selection of TKIs, proper monitoring during treatment and assessment of survival outcomes and treatment response among affected patients.⁷

In the present study, the median age of CML patients at the time of diagnosis was 43.5 years; this is younger in comparison to patients reported in Western populations.^{13,14,17} Similar findings have been reported in other Iraqi epidemiological studies; however, unlike the current study, these previous reports described CML as being more common among males than females.^{22,23} As the median age of the patient population was younger in the present study, CCI scoring was age-adjusted for assessment purposes. As with previous studies from other countries, diabetes was found to be the most common comorbidity reported among CML patients in the current study.^{13,14,17,20}

Previous research suggests that higher CCI scores are significantly associated with lower OS probabilities, with inverse associations noted between CCI scores and OS among chronic phase CML patients in Japan, Italy and Germany.^{13,14,19} Saussele *et al.* observed that higher CCI scores were significantly associated with lower OS probabilities ($P < 0.001$), even after excluding age from the CCI calculation.¹³ The presence of comorbidities at the time of diagnosis has also been associated with poor survival outcomes among CML patients being treated with TKIs, with comorbidities having more impact on survival than the disease itself.¹² Similarly, Imataki *et al.* documented a significant log-rank association between comorbidity at diagnosis and survival among CML patients on TKI treatment ($P = 0.0136$).²⁰ Breccia *et al.* also reported that comorbidities had a similar impact on median OS and non-CML-related deaths.¹⁹

In contrast, the present retrospective analysis did not reveal a significant difference in mortality rates among CML patients according to CCI scores. Instead, the study found that 69.6% of deaths in the patient population were due to CML and not the presence or severity of comorbidities. This was in contrast to the findings of Saussele *et al.* and Uemura *et al.*, who reported that mortality among CML patients was more dependent on comorbidities than CML.^{13,14} This difference in findings may be because of the more aggressive behaviour of CML among the Iraqi people. As such, mutational studies are recommended for

Iraqi patients with primary and secondary failure to investigate the nature of CML in this population.

Other prognostic scales available for use among CML patients include the Sokal Index, Hasford Risk Score, Karnofsky Performance Scale Index (KPSI) and the European Treatment and Outcome Study (EUTOS) score.^{24–26} It is likely that varying results regarding OS in CML patients reported by different studies is due to the selection of disparate prognostic markers and scoring systems, thereby highlighting the need for a uniform prognostic scoring system for CML patients. Of the CCI, EUTOS and KPSI scales, Saussele *et al.* found that CCI was the most powerful predictor for OS in German patients with CML.¹³ Similarly, the authors of the current study plan to compare the aforementioned prognostic scores among CML patients being treated with TKIs at the Basra Oncology & Haematology Centre. Additionally, further research evaluating the application of the CCI tool among older patients is necessary.

The limitations of the current study include its retrospective design, the limited sample size and the lack of availability of data regarding management of the comorbidities identified in the study population. Although there was no correlation between CCI and OS, further analysis using a larger dataset is needed to generate stronger evidence for this finding. Additionally, future studies should investigate the correlation between age at disease onset and patient outcome.

Conclusion

The median age of CML patients in Basra was lower than epidemiological data reported from other countries. Moreover, the CCI score was not significantly associated with OS; for the majority of patients, disease progression due to CML itself was the cause of death, rather than the presence or severity of comorbidities. Further research into the development of more accurate region-specific prognostic scoring systems to evaluate risk-based outcomes among CML patients would facilitate individualised treatment for this population.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

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