Prognostic scoring systems and comorbidities in chronic myelomonocytic leukaemia: a nationwide population-based study

Daniel Moreno Berggren, Matilda Kjellander, Marie Engvall, Fryderyk Lorenz, Bengt Rasmussen, Eva Hellström-Lindberg, Martin Jädersten, Johanna Ungerstedt and Elisabeth Ejerblad

Department of Medical Science, Section of Hematology, Uppsala University, Uppsala, Sweden
Center for Hematology and Regenerative Medicine, Department of Medicine Huddinge, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden
Section for Haematology and Coagulation, Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden
Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden
Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital, Lund, and School of Medical Sciences, Örebro University Hospital, Örebro, Sweden

Summary

Outcomes in chronic myelomonocytic leukaemia (CMML) are highly variable and may be affected by comorbidity. Therefore, prognostic models and comorbidity indices are important tools to estimate survival and to guide clinicians in individualising treatment. In this nationwide population-based study, we assess comorbidities and for the first time validate comorbidity indices in CMML. We also compare the prognostic power of: the revised International Prognostic Scoring System (IPSS-R), CMML-specific prognostic scoring system (CPSS), MD Anderson Prognostic Scoring System (MDAPS) and Mayo score. In this cohort of 337 patients with CMML, diagnosed between 2009 and 2015, the median overall survival was 21.3 months. Autoimmune conditions were present in 25% of the patients, with polymyalgia rheumatica and Hashimoto’s thyroiditis being most common. Of the tested comorbidity indices: the Charlson Comorbidity Index (CCI), Haematopoietic cell transplantation-specific Comorbidity Index (HCT-CI) and Myelodysplastic Syndrome-Specific Comorbidity Index (MDS-CI), CCI had the highest C-index (0.62) and was the only comorbidity index independently associated with survival in multivariable analyses. When comparing the prognostic power of the scoring systems, the CPSS had the highest C-index (0.69). In conclusion, using ‘real-world’ data we found that the CCI and CPSS have the best prognostic power and that autoimmune conditions are overrepresented in CMML.

Keywords: chronic myelomonocytic leukaemia (CMML), prognostic scores, comorbidity index, population-based study, CMML-specific prognostic scoring system (CPSS).

Introduction

Chronic myelomonocytic leukaemia (CMML) is a rare clonal haematopoietic stem cell disorder with a yearly incidence of 0.3–0.7 per 100 000 inhabitants. In 1976 CMML was recognised as a subset of myelodysplastic syndrome (MDS) and a proliferative subtype (MP-CMML) were described based on a white blood cell count (WBC) of ≤13 x 10^9/l and >13 x 10^9/l, respectively. In the World Health Organization (WHO) classification of 2008, CMML was included in the group of myelodysplastic/myeloproliferative neoplasms (MDS/MPN). The update of 2016 includes three groups of blast percentages instead of the former two.
Survival ranges from months to decades, with a median of around 13 months. The 5-year cumulative progression to acute myeloid leukaemia (AML) is reported to be 21–29%. Therapy-related CMML (t-CMML) is in accordance with therapy-related MDS reported to have more high-risk cytogenetics and a shorter overall survival (OS).

As outcome in CMML is highly variable, prognostic models are important tools to estimate survival and to guide clinicians in individualising treatment. The most accepted scoring system for MDS, the Revised International Prognostic Scoring System (IPSS-R) has been used for MD-CMML, but is not considered valid for MP-CMML. Several CMML-specific scoring systems have been developed including the MD Anderson Prognostic Scoring System (MDAPS), the CMML-Specific Prognostic Scoring System (CPSS) and the Mayo score.

Somatic mutations are found in approximately 90% of patients with CMML, mutations TET2, ASXL1 and SRSF2 are the most common. Specific combinations of mutated genes have been identified as typical for CMML, and selected genes provide useful prognostic information. More recent scores, that is, CPSS-Molecular and Mayo Molecular model are important tools to estimate survival and to guide clinicians in individualising treatment.

Most patients with CMML are elderly, with a median age of around 77 years at diagnosis; thus comorbidities might have an important impact on survival and treatment. Comorbidities measured by the Charlson Comorbidity Index (CCI), Haematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) and MDS-Specific Comorbidity Index (MDS-CI) have an independent impact on survival in MDS, including cohorts with a small percentage of patients with CMML. The HCT-CI has been validated in patients with CMML undergoing allogeneic stem-cell transplantation (HSCT). However, to our knowledge, there has been no previous study examining the impact of comorbidity indices in a larger cohort of unselected patients with CMML.

In a nationwide population-based cohort of 337 patients, we performed a ‘real-world’ comparison of scoring systems and comorbidity indices in CMML. As no mutational data were available, the selected prognostic scoring systems were: the IPSS-R, CPSS, MDAPS and Mayo score. For assessing the impact of comorbidity we used the CCI, HCT-CI and MDS-CI. We also present detailed data on incidence of CMML, clinical characteristics including cytogenetics, treatments, comorbidities, AML-transformations and survival.

Patients and methods

CMML cases diagnosed between 2009 and 2015 and reported to the Swedish MDS register were included. The Swedish nationwide MDS register includes patients with MDS but also MDS/MPN, where CMML is the largest group. The register is described in detail elsewhere. For the time period of this study the coverage of the MDS register against the Swedish Cancer Register was 97%.

A detailed retrospective chart review was carried out collecting information on laboratory parameters at diagnosis, prior history of chemotherapy and irradiation, comorbidities, transfusions, diagnostic procedures including cytogenetics and bone marrow morphology, and treatments. Cytogenetic analyses were performed at the regional clinical genetic laboratories according to local standards and reviewed centrally by one of the investigators.

The study encompassed patients with CMML and t-CMML receiving all types of treatment, patients were censored at HSCT. Information was obtained from the Swedish Population Register at 6 December 2018 in order to calculate OS. In addition to the chart review, information on AML transformation was collected from the Swedish AML Register. Comorbidities were defined as in the original publications of the CCI, HCT-CI and MDS-CI. End of follow-up was defined as the earliest of the date of death, date of HSCT, emigration or 6 December 2018. This study was approved by the Ethics Committee of Uppsala University.

Statistical analysis

To assess the distribution of baseline patient characteristics, standard descriptive techniques were used, including chi-squared test and Wilcoxon rank-sum test. OS was defined as the time from diagnosis to end of follow-up and analysed using the Kaplan–Meier approach. The risk of AML was calculated using the cumulative incidence function to account for competing risks (deaths). A Cox regression model was constructed to explore the independent effect of the comorbidity indices on survival. Comorbidity index scores were analysed as a continuous variable. Significant variables from the univariate analyses were considered in the multivariate analyses. The final Cox regression model was constructed using backward elimination. To assess the Cox model, Akaike information criterion (AIC) was calculated. A $P < 0.05$ was considered statistically significant.

The prognostic power of the prognostic scoring systems and comorbidity indices was evaluated with the Harrell’s concordance (C) index. The C-index ranges between 0.5 and 1, where 1 stands for perfect discrimination and 0.5 for no discrimination at all. When comparing C-indices the approach described by Le Kang was used. All analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and the Statistical Package for the Social Sciences (SPSS®) for Windows, version 24 (SPSS Inc., IBM Corp., Armonk, NY, USA).

Results

Study population and incidence

A total of 359 patients with CMML, diagnosed between 2009 and 2015, were reported to the register. Of these, 22 patients were excluded; 15 patients were considered having primary
AML, five did not fulfill criteria for CMML and two were diagnosed before 2009. The final cohort of 337 patients corresponds to a crude annual incidence of 0.51 per 100 000 inhabitants. The patients were diagnosed at 53 different hospitals, 150 of them (45%) at university hospitals.

Patient characteristics at diagnosis

Baseline characteristics and their impact on survival are presented in Table I. MP-CMML was diagnosed in 67% of the patients. A history of treatment with chemotherapy and/or irradiation was reported in 20 patients, these patients with t-CMML had a similar median age as those with de novo CMML but slightly higher rates of high-risk cytogenetics (data not shown). Karyotyping was performed at diagnosis in 242 patients (72%), 75 of whom (31%) were abnormal. Among those with an available karyotype, 14% were in the high-risk group according to the Spanish cytogenetic score and trisomy 8 was the most common abnormality (Table I). The median age was older among patients lacking karyotyping (83 years).

Treatments

The most common treatment was hydroxyurea, which was given to 153 patients (45%); of these, 37 (24%) had splenomegaly at diagnosis and 131 (86%) had WBC of >13 × 10^9/l. Erythropoiesis-stimulating agents were initiated in 68 patients in comparison with 20 patients that did not receive HSCT. However, patients receiving HSCT were significantly younger, with a median (range) age of 57 (31–68) years, and had less comorbidity. At the end of the study 13 transplanted patients (59%) were still alive after a median (range) follow-up of 67 (42–119) months.

Overall survival and comparison of prognostic scoring systems

The median follow-up for surviving patients was 59 months. The 2-year OS was 46% and at end of study 272 (81%) patients had died. There was no difference in OS between patients diagnosed at university hospitals (median 23.0 months) and local hospitals (median 19.5 months). In Table II we present the distribution and survival according to risk group for the IPSS-R, CPSS, MDAPS and Mayo score. The 96 patients for which we could not calculate the CPSS had a median survival of 14.9 months, shorter than for the whole cohort; the main reason for missing data was lack of cytogenetics. These patients were significantly older and had a median age of 83 years. Kaplan–Meier curves for OS are presented in Fig 1.

The C-index of the CPSS, MDAPS and Mayo score was 0.69, 0.65 and 0.66, respectively (Table II), these differences were non-significant. The IPSS-R had a C-index of 0.60, significantly lower than the CPSS (P = 0.004). The IPSS-R was also tested in the subgroup of patients with MD-CMML, but the prognostic power did not increase. In subgroup analysis of patients aged <70 years the C-indices were 0.78, 0.67, 0.66 and 0.65 for the CPSS, IPSS-R, MDAPS and Mayo score, respectively. The differences between the CPSS and the other scoring systems were statistically significant. For patients aged ≥70 years all scoring systems were borderline significantly better than the IPSS-R.

Progression to AML and comparison of prognostic scoring systems

During the follow-up, 62 patients (18%) progressed to AML after a median of 16 months. The median OS after transformation to AML was 83 days and at study end only three patients were alive. The median age at transformation was 72 years, and 69% were male. Two patients with transformation underwent HSCT; these had a median OS of 8.5 months.

When comparing the ability to predict evolution to AML, the C-index of the CPSS, IPSS-R MDAPS and Mayo score was 0.68, 0.64, 0.66 and 0.62, respectively; these differences were non-significant. Kaplan–Meier curves for cumulative incidence of AML for different risk groups of the IPSS-R, CPSS, MDAPS and Mayo score are depicted in Fig 2.

Comorbidity

Cardiac disorders were most frequent, found in 115 patients (34%) (Table III). Polymyalgia rheumatica (PMR) and Hashimoto’s thyreoiditis were the most common autoimmune conditions. A prior solid tumour was found in 60 patients (18%), the most frequent cancer types were: prostate (n = 19), breast (n = 8) and colorectal (n = 8). In univariate analysis arrhythmia, heart failure, moderate-to-severe renal disease and Hashimoto’s thyreoiditis were significantly associated with shorter survival.

We applied the CCI, HCT-CI and MDS-CI to all patients. The distribution, median OS and hazard ratio for the whole cohort and for a subgroup of lower-risk CMML (CPSS low or intermediate-1) are shown in Table IV. The C-index for the CCI, HCTCI and MDS-CI was 0.62, 0.61 and 0.59, respectively; these differences were statistically non-significant. In subgroup analysis of lower-risk CMML the C-index of the CCI and HCT-CI improved. The difference in C-index between the CCI and MDS-CI for lower-risk CMML was significant (P = 0.03). Kaplan–Meier curves depicting OS for the comorbidity indices for the whole cohort and for lower-risk CMML are presented in Fig 3A,B.
Table I. Characteristics and median overall survival (OS) in months.

| Characteristic                      | N (%)     | Median OS (95% CI)* |
|-------------------------------------|-----------|---------------------|
| All patients                        | 337 (100) | 21.3 (17.8–24.8)    |
| Sex                                 |           |                     |
| Male                                | 207 (61)  | 22.5 (18.4–26.6)    |
| Female                              | 130 (39)  | 20.4 (15.3–25.4)    |
| Age at diagnosis, years             |           |                     |
| Median (range)                      | 76 (28–97)|                     |
| <70                                 | 94 (28)   | 35.4 (24.7–46.1)    |
| 70–80                               | 110 (33)  | 20.4 (14.7–26.2)    |
| ≥80                                 | 133 (39)  | 15.3 (12.0–18.6)    |
| Haemoglobin, g/l                    |           |                     |
| Median (range)                      | 108 (30–168)|     |
| <100                                | 108 (32)  | 11.9 (9.4–14.4)     |
| ≥100                                | 229 (68)  | 27.2 (22.4–32.0)    |
| WBC, ×10⁹/l                         | 192 (1–213–2)| |
| ≤13                                 | 123 (37)  | 35.7 (26.5–44.9)    |
| >13                                 | 214 (63)  | 18.2 (14.5–21.8)    |
| Platelet count, ×10⁹/l              |           |                     |
| Median (range)                      | 113 (8–928)|     |
| <100                                | 143 (42)  | 20.3 (14.9–25.7)    |
| ≥100                                | 194 (58)  | 22.5 (18.6–26.5)    |
| Lymphocyte count, ×10⁹/l            | 2.5 (0.1–24)|     |
| ≤2.5                                | 162 (48)  | 24.5 (18.5–30.5)    |
| >2.5                                | 162 (48)  | 20.3 (17.3–23.2)    |
| Missing data                         | 13 (4)    | –                   |
| Monocyte count, ×10⁹/l              | 3.9 (0.1–91.0)|     |
| ≤10                                 | 276 (82)  | 26.6 (21.0–32.2)    |
| >10                                 | 61 (18)   | 15.0 (9.2–20.7)     |
| RBC transfusion dependency at diagnosis |        |                     |
| No                                  | 231 (69)  | 28.7 (23.6–33.8)    |
| Yes                                 | 106 (32)  | 11.4 (9.7–13.1)     |
| Platelet transfusion dependency at diagnosis |        |                     |
| No                                  | 305 (91)  | 23.4 (19.8–27.1)    |
| Yes                                 | 32 (9)    | 11.1 (9.0–13.2)     |
| Circulating blasts                  |           |                     |
| No                                  | 249 (74)  | 26.1 (20.6–31.6)    |
| Yes                                 | 81 (24)   | 11.9 (9.9–13.8)     |
| Missing data                         | 7 (2)     | –                   |
| WHO subtype                         |           |                     |
| CMML 0                              | 185 (54.9)| 23.0 (18.8–27.2)    |
| CMML 1                              | 83 (24.6)| 21.0 (13.8–28.2)    |
| CMML 2                              | 68 (20.2)| 18.7 (9.0–28.4)     |
| Missing data                         | 1 (0.3)   | –                   |
| LDH, µkat/l                         | 4.0 (1.6–47.6)|     |
| <4                                  | 134 (40)  | 29.1 (21.1–37.1)    |
| ≥4                                  | 139 (41)  | 17.4 (11.2–23.5)    |
| Missing data                         | 64 (19)   | 18.8 (12.2–25.4)    |
| Karyotyping performed               |           |                     |
| Yes                                 | 242 (72)  | 25.3 (19.9–30.6)    |
| No                                  | 95 (28)   | 15.0 (8.9–21.0)     |

Table I. (Continued)

| Characteristic                      | N (%)     | Median OS (95% CI)* |
|-------------------------------------|-----------|---------------------|
| Normal                              | 167 (69)  | 29.7 (23.0–36.5)    |
| Abnormal                            | 75 (31)   | 15.0 (9.8–20.2)     |
| -Y                                  | 11 (4)    | 68.5 (17.3–119.8)   |
| Trisomy 8†                          | 19 (8)    | 20.7 (10.0–31.4)    |
| Chromosome 7 abnormalities†         | 9 (4)     | 11.4 (0.7–22.1)     |
| All other single/                   |           |                     |
| double abnormalities                | 29 (12)   | 15.3 (9.0–21.6)     |
| Complex karyotype                   | 7 (3)     | 9.0 (2.9–15.2)      |
| Spanish cytogenetic score‡          |           |                     |
| Low                                 | 178 (74)  | 29.9 (22.8–37.0)    |
| Intermediate                         | 29 (12)   | 15.2 (9.0–21.6)     |
| High                                | 35 (14)   | 12.2 (8.9–15.6)     |
| Type of CMML                         |           |                     |
| Primary CMML                         | 313 (93)  | 21.0 (17.4–24.6)    |
| Therapy-related CMML                | 24 (7)    | 23.4 (14.9–32.0)    |

CI, confidence interval; WBC, white blood cell count; RBC, red blood cell; LDH, lactate dehydrogenase.
†Not shown if fewer than 20 patients were included.
‡Including cases with one more abnormality.
§Low: Normal or isolated –Y. Intermediate: All other abnormalities. High: Trisomy 8 or abnormalities of chromosome 7 or complex karyotype.

Table II. Risk score classification, survival in months, hazard ratios (HRs) and discriminative power of the scoring systems.

| Overall survival                      | N | Median | HR 95% CI | C-index |
|---------------------------------------|---|--------|-----------|---------|
| All patients                          | 337| 21.3   | 1.00 Ref. | 0.60    |
| IPPS-R                                |   |        |           |         |
| Very low risk                         | 46 | 25.3   | 1.00 Ref. | 0.60    |
| Low risk                              | 95 | 30.8   | 1.03 0.68–1.56 |
| Intermediate risk                     | 56 | 23.9   | 1.35 0.86–2.12 |
| High risk                             | 38 | 12.4   | 1.80 1.02–2.93 |
| Very high risk                        | 6  | 11.1   | 3.73 1.43–9.73 |
| CPSS                                  |   |        |           |         |
| Low                                   | 46 | 52.2   | 1.00 Ref. | 0.69    |
| Intermediate 1                        | 94 | 26.3   | 1.76 1.12–2.75 |
| Intermediate 2                        | 86 | 18.7   | 3.11 1.99–4.87 |
| High                                  | 15 | 10.4   | 4.62 2.32–9.22 |
| MDAPS                                 |   |        |           |         |
| Low                                   | 164| 29.7   | 1.00 Ref. | 0.65    |
| Intermediate 1                        | 91 | 21.3   | 1.42 1.06–1.91 |
| Intermediate 2                        | 55 | 12.4   | 2.51 1.79–3.53 |
| High                                  | 18 | 10.4   | 3.43 2.01–5.85 |
| Mayo                                  |   |        |           |         |
| Low                                   | 98 | 31.5   | 1.00 Ref. | 0.66    |
| Intermediate 1                        | 122| 25.4   | 1.42 1.04–1.94 |
| High                                  | 115| 12.4   | 2.60 1.89–3.56 |

IPPS-R, International Prognostic Scoring System Revised; CPSS, CMML-specific prognostic scoring system; MDAPS, MD Anderson Prognostic Scoring System; HR, hazard ratio; CI, confidence interval.

© 2020 The Authors. British Journal of Haematology published by British Society for Haematology and John Wiley & Sons Ltd. British Journal of Haematology, 2021, 192, 474–483
Uni- and multivariate analysis and risk of death

In univariate analysis, age, risk group according to the CPSS/MDAPS/Mayo score, score on the CCI/HCTCI/MDS-CI, platelet count of <50 \(10^9/l\), lactate dehydrogenase of >4 \(\mu\)kat/l and a monocyte count of >10 \(10^9/l\) were associated with worse outcome. However, in multivariate analyses only age, monocyte count, CPSS-group and CCI-score were significantly associated with OS and thus included in the final Cox model (Table V). We chose to include the CPSS in the model as it had the highest C-index of the tested scoring systems. All three comorbidity indices were tested separately, but only the CCI was significantly associated with survival in the Cox model. When including the CCI in the Cox model the AIC improved, indicating a better fitted model.

Discussion

As several prognostic scoring systems exist for CMML, we compared the IPSS-R, CPSS, MDAPS and Mayo score. The CPSS had a slightly better prognostic power than the MDAPS and Mayo score. In our present setting, the IPSS-R had the lowest C-index, significantly lower than the CPSS. We conclude that the IPSS-R should not be used in CMML.

When we stratified for age <70 years, the C-index of the CPSS increased and had a significantly better prognostic power than all other scoring systems. We find this worth highlighting; it is particularly important with accurate risk scoring in this age group where HSCT may be considered.

The superiority of the CPSS is consistent with a smaller study by Calvo et al., where the CPSS had a slightly better C-index than the MDAPS and Mayo score. An international consortium based on eight tertiary centres validated prognostic scoring systems. In their C-index analysis the CPSS and IPSS-R had the highest values, the latter result conflicting with ours. Compared to our present cohort, theirs had a lower median age, longer OS and, fewer patients with MP-CMML, which might be in favour of the IPSS-R. Several newer prognostic scores including mutations have been developed and also recommended by European CMML guidelines. As our present study included cases diagnosed between 2009 and 2015, we lack mutational data and could thus not include these newer scores, a limitation of our study.

During the study period, 18% of the patients transformed to AML, a slightly lower proportion than previously reported. Patients developing AML within 2 months after diagnosis should not be reported to the MDS Register, as there might be diagnostic difficulties to distinguish evolving primary AML with myelodysplastic changes from MDS. However, this might lead to an underestimation of the transformation rate. There were no significant differences between systems in predicting transformation to AML. The survival of patients transforming to AML was dismal, with virtually no long-term survivals, highlighting the need for therapies reducing the risk of transformation to AML.
As in previous studies, one-third of our patients had an abnormal karyotype. Isolated loss of chromosome Y was associated with a better survival, in line with the cytogenetic classification for MDS but not for CMML. In the Spanish Cytogenetic Score, trisomy 8 belongs to the high-risk group. However, our present study patients with trisomy 8 had a median survival more similar to the intermediate group, supporting previous reports suggesting that trisomy 8 should be considered an intermediate-risk aberration. Patients with a complex karyotype have a dismal survival, and it appears that they constitute a true high-risk cytogenetic group. Patients with lack of data on cytogenetics where older and had a survival similar to the intermediate group in the Spanish Cytogenetic Score. Death within 3 months occurred in 15% of patients lacking cytogenetics, this could in part be the reason for the lack of cytogenetics, but we believe that the main reason is a limited diagnostic evaluation mainly due to age. Collaborative efforts to create larger databases should be able to further clarify the prognostic role of different cytogenetic aberrations together with mutations in CMML.

We did not find that patients with t-CMML had a worse outcome than those with de novo CMML, which others have reported. However, only 24 patients (7%) had t-CMML in our present cohort.

The prevalence of autoimmune conditions was 25%, a clear overrepresentation as the lifetime prevalence in the general population is reported to be 3%. This association is previously reported from smaller or more restricted cohorts of CMML, as well as for AML and MDS. PMR was found in 8% of the patients as compared to a lifetime risk of 2% in the general population. As PMR is a clinical diagnosis, an alternative explanation for the high prevalence might be a more general para-malign phenomenon or pain associated with CMML itself. Hashimoto’s thyroiditis was found in 7% of the patients as compared to around 1% in the general public, this overrepresentation is consistent with Peker et al., who found hypothyroidism in 8% of patients, although not classifying them as autoimmune. It is proposed that chronic inflammation may act as a trigger and driver of clonal evolution, suggesting a pathogenic role in MPNs and CMML. Moreover, chronic inflammation from autoimmune disease might act as a link between cardiovascular disease and CMML, several
autoimmune conditions have increased arteriosclerosis and cardiovascular morbidity. In fact, cardiac disease was a common comorbidity in our present study and ischaemic heart disease the most frequent condition. We find this interesting in light of that TET2 mutations are common in CMML, as well as in clonal haematopoesis of indeterminate potential, and highly associated with coronary heart disease. Whether there is a connection between the cardiovascular comorbidity and TET2 mutations in CMML remains to be determined.

We found that the CCI had a slightly higher C-index than the HCT-CI and MDS-CI. The C-index of the CCI and HCT-CI was higher in patients with lower-risk CPSS. Thus, comorbidity has an impact on survival in lower-risk disease, whereas the poor prognosis of high-risk CMML makes the additional effect of comorbidity less important. Similar results have been shown for MDS. There have been comparisons of the CCI, HCT-CI and MDS-CI in cohorts of patients with MDS, where the CCI and MDS-CI were superior to the HCT-CI. Another study reported that the CCI had a slightly better prognostic power than MDS-CI. Although the differences are small, the fact that the CCI was significant in multivariate analysis and had the highest C-index in the lower-risk disease group makes us conclude that in our present cohort the CCI was the most powerful comorbidity index. One reason that the CCI was superior to the MDS-CI could be that it includes more comorbidities, an index that captures the high burden of comorbidity might have a better prognostic power. However, the simplicity of the MDS-CI can be an advantage in clinical practice, and the sometimes outdated definitions of the comorbidities in the CCI can be a potential problem.

The collection of data regarding comorbidities was done by chart review and not through registries, and could result in an underestimation of the comorbidity burden, although a full medical history was available from most hospitals.

**Table III.** Distribution of the most common comorbidities and univariate analysis of overall survival.

| Comorbidity                               | Prevalence, n (%) | HR (95% CI) |
|-------------------------------------------|------------------|-------------|
| Heart failure                             | 24 (7)           | 2.38 (1.50–3.64) |
| Valvular heart disease                    | 15 (4)           | 1.10 (0.61–1.86) |
| Any autoimmune condition*                | 83 (25)          | 1.13 (0.86–1.49) |
| Polymyalgia rheumatica                    | 28 (8)           | 1.19 (0.79–1.78) |
| Hashimoto’s thyroiditis                   | 23 (7)           | 1.60 (1.02–2.50) |
| Psoriasis/psoriatic arthritis            | 17 (5)           | 0.72 (0.39–1.32) |
| Rheumatoid arthritis                     | 10 (3)           | 1.60 (0.85–3.01) |
| Inflammatory bowel disease†              | 5 (1.5)          | 0.94 (0.30–2.95) |
| Prior solid tumour                       | 60 (18)          | 1.02 (0.74–1.41) |
| Diabetes                                  | 46 (14)          | 0.97 (0.68–1.38) |
| Pulmonary disease                         | 35 (11)          | 1.28 (0.86–1.91) |
| Stroke/transient ischaemic attack         | 29 (9)           | 1.18 (0.79–1.77) |
| Moderate-to-severe renal disease          | 23 (7)           | 2.53 (1.61–3.96) |
| Peripheral vascular disease               | 17 (5)           | 1.48 (0.87–2.49) |
| Psychiatric illness/dementia             | 17 (5)           | 1.11 (0.64–1.95) |
| Hepatic disease                           | 10 (3)           | 1.03 (0.49–2.19) |

*Including: polymyalgia rheumatica, Hashimoto’s thyroiditis, psoriasis/psoriatic arthritis, rheumatoid arthritis, Crohn’s disease, Grave’s disease, Mb Still, autoimmune haemolytic anaemia, autoimmune hepatitis, iritis, immune thrombocytopenia, Behceter’s disease, ulcerative colitis, Behcet’s disease, dermatomyositis, Ig A nephritis, aortitis, giant-cell arteritis, unspecified vasculitis and sarcoidosis.

†Four cases of Crohn’s disease and one of ulcerative colitis.

**Table IV.** Comorbidity index classification, overall survival in months, hazard ratios and discriminative power of comorbidity indices for all patients and for CPSS low + Int-1.

| Overall survival                      | CPSS low + Int-1 |
|---------------------------------------|------------------|
| All patients                          | CCI              | HCTCI             | MDS-CI            | N | Median | HR  | 95% CI  | C-index | N | Median | HR  | 95% CI  | C-index |
|                                       |                  |                   |                  | 0 | 25-3   | 1-00 | Ref. | 0.62 | 68 | 50-6 | 1-00 | Ref. | 0.68 |
| CCI                                   | 0                | 149               | 1-00             | Ref. | 0.62 |
|                                       | 1–2              | 140               | 1-26             | 0.97–1.64 | 59 | 30-8 | 1-75 | 1-13–2-71 | 0.64 |
|                                       | >2               | 48                | 2-16             | 1-50–3-10 | 13 | 18-8 | 2-98 | 1-51–3-87 | 0.64 |
| HCTCI                                 | 0                | 118               | 1-00             | Ref. | 0.61 |
|                                       | 1–2              | 103               | 1-23             | 0-90–1-67 | 43 | 34-3 | 1-53 | 0-93–2-53 | 0.64 |
|                                       | >2               | 116               | 1-54             | 1-15–2-06 | 39 | 27-3 | 1-94 | 1-19–3-18 | 0.64 |
| MDS-CI                                | 0                | 198               | 1-00             | Ref. | 0.59 |
|                                       | 1–2              | 112               | 23-0             | 0-92–1-54 | 43 | 36-9 | 1-27 | 0-82–1-97 | 0.59 |
|                                       | >2               | 27                | 9-4              | 1-11–2-69 | 8 | 19-5 | 1-63 | 0-70–3-81 | 0.59 |

CCI, Charlson Comorbidity Index; HCTCI, Haematopoietic Cell Transplantation-Specific Comorbidity Index; MDS-CI, Myelodysplastic Syndrome-Specific Comorbidity Index; HR, hazard ratio; CI, confidence interval.
some patients with lower WBC counts have been misdiagnosed as MDS instead of CMML.49

The present study offers data from a large nationwide cohort of patients with CMML. We found that comorbidity is common and that there is an overrepresentation of autoimmune conditions, which needs to be further studied regarding causality, common risk factors and effect on prognosis. Furthermore, we show that comorbidity adds prognostic information in patients with lower-risk CMML, and that the CCI may give more prognostic information than the HCT-CI and MDS-CI. We conclude that, of the tested prognostic scoring systems, the CPSS appears to have a slightly better prognostic capacity than the MDAPS and Mayo score. In our present cohort, the IPSS-R was not a valuable prognostic tool. Data from population-based registries will be of great value in the continuous efforts to improve prognostication and, ultimately, outcomes for patients with CMML.

**Acknowledgements**

The authors wish to thank all Swedish haematologists who have reported patients to the Swedish MDS Register. The authors also appreciate the work of data managers at the respective RCC.

**Author contributions**

Daniel Moreno Berggren preformed the research, collected and analysed the data and wrote the paper. Matilda Kjellander collected and analysed the data. Ellen Backlund collected data. Marie Engvall reviewed and analysed the cytogenetic data. Hege Garelius, Fryderyk Lorenz, Lars Nilsson and Bengt Rasmussen are local coordinators of the Swedish MDS...
Conflict of Interest
The authors have no conflicts of interest to declare.

References
1. Benzarti S, Daskalakis M, Feller A, Bacher VU, Schnegg-Kaufmann A, Rufer A, et al. Trends of incidence and survival of patients with chronic myelomonocytic leukemia between 1999 and 2014: a comparison between Swiss and American population-based cancer registries. Cancer Epidemiol. 2019;59:51–7.
2. Roman E, Smith A, Appleton S, Crouch S, Kelly R, Kinsey S, et al. Myeloid malignancies in the real-world: occurrence, progression and survival in the UK’s population-based Haematological Malignancy Research Network 2004–15. Cancer Epidemiol. 2016;42:386–98.
3. Sant M, Allemani C, Teranu C, De Angelis R, Capocaccia R, Vinser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116:3724–34.
4. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the acute leukemias. French-American-British (FAB) co-operative group. Br J Haematol. 1976;33:451–8.
5. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick H, et al. The chronic myeloid leukemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukemia. Proposals by the French-American-British Cooperative Leukaemia Group. Br J Haematol. 1994;87:746–54.
6. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114:937–51.
7. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–405.
8. Onda F, Kantarjian HM, Smith TL, Ball G, Keating MJ, Estey EH, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. Blood. 2002;99:840–9.
9. Such E, Germain U, Malcovati L, Cervera J, Kuendgen A, Della Porta MG, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood. 2013;121:3005–15.
10. Moreno Berggren D, Folkvalljon Y, Engvall M, Sundberg J, Lambe M, Antunovic P, et al. Prognostic scoring systems for myelodysplastic syndromes (MDS) in a population-based setting: a report from the Swedish MDS register. Br J Haematol. 2018;181:614–27.
11. Patnaik MM, Vallapureddy R, Talniz FF, Hanson CA, Ketterling RP, Laslo TL, et al. Therapy related-chronic myelomonocytic leukemia (CMMML): Molecular, cytogenetic, and clinical distinctions from de novo CMMML. Am J Hematol. 2018;93:65–73.
12. Takahashi K, Pemmaraju N, Strati P, Nogues-Gonzalez G, Ning J, Bueso-Ramos C, et al. Clinical characteristics and outcomes of therapy-related chronic myelomonocytic leukemia. Blood. 2013;122:2807–11.
13. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120:2454–65.
14. Such E, Cervera J, Costa D, Sole F, Vallespi T, Luno E, et al. Cytogenetic risk stratification in chronic myelomonocytic leukemia. Haematologica. 2011;96:375–83.
33. Valent P, Orazi A, Savona MR, Patnaik MM, Onida F, van de Loosdrecht AA, et al. Proposed diagnostic criteria for classical chronic myelomono- 
cytic leukemia (CMML), CMML variants and pre-CMML conditions. 
Haematologica. 2019;104:1935–49.
34. Tang G, Zhang L, Fu B, Hu J, Lu X, Hu S, et al. Cytogenetic risk stratifi-
cation of 417 patients with chronic myelomonocytic leukemia from a sin-
gle institution. Am J Hematol. 2014;89:813–8.
35. Schanz J, Tuchler H, Sole F, Mallo M, Luno E, Cervera J, et al. New compre-
hensive cytogenetic scoring system for primary myelodysplastic syndromes 
(MDS) and oligoblastic acute myeloid leukemia after MDS derived from an 
international database merge. J Clin Oncol. 2012;30:820–9.
36. Wassie EA, Itzykson R, Lasho TL, Kosmider O, Finke CM, Hanson CA, 
et al. Molecular and prognostic correlates of cytogenetic abnormalities in 
chronic myelomonocytic leukemia: a Mayo Clinic-French Consortium 
Study. Am J Hematol. 2014;89:1111–5.
37. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. 
Autoimmun Rev. 2003;2:119–25.
38. Elbaek MV, Sorensen AL, Hasselbalch HC. Chronic inflammation and 
autoimmunity as risk factors for the development of chronic myelomonocy-
tic leukemia? Leuk Lymphoma. 2016;57:1793–9.
39. Peker D, Padron E, Bennett JM, Zhang X, Horna P, Epling-Burnette PK, 
et al. A close association of autoimmune-mediated processes and autoim-
muine disorders with chronic myelomonocytic leukemia: observation from a 
single institution. Acta Haematol. 2015;133:249–56.
40. Zahid MF, Barracon D, Lalloo TH, Finke C, Ketterling RP, Gagat N, et al. Spec-
trum of autoimmune diseases and systemic inflammatory syndromes in patients 
with chronic myelomonocytic leukemia. Leuk Lymphoma. 2017;58:1488–93.
41. Kristinsson SY, Bjorkholm M, Hultcrantz M, Derolf AR, Landgren O, 
Goldin LR. Chronic immune stimulation might act as a trigger for the 
development of acute myeloid leukemia or myelodysplastic syndromes. J 
Clin Oncol. 2011;29:2897–903.
42. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Errante FC, Warr-
ington KJ, et al. The lifetime risk of adult-onset rheumatoid arthritis and 
other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 
2011;63:633–9.
43. Hasselbalch HC. Chronic inflammation as a promotor of mutagenesis 
in essential thrombocythemia, polycythemia vera and myelofibrosis. A 
human inflammation model for cancer development? Leuk Res. 
2013;37:214–20.
44. Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoim-
mune diseases. Nat Clin Pract Rheumatol. 2006:2:99–106.
45. Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E, et al. 
Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N 
Engl J Med. 2017:377:111–21.
46. Steensma DP, Bejar R, Jaiswal S, Lindsley RC, Sekeres MA, Hasserjian RP, 
et al. Clonal hematopoiesis of indeterminate potential and its distinction 
from myelodysplastic syndromes. Blood. 2015;126:9–16.
47. Sperr WR, Wimazal F, Kundi M, Baumgartner C, Nosslinger T, Makrai A, 
et al. Comorbidity as prognostic variable in MDS: comparative evaluation 
of the HCT-CI and CCI in a core dataset of 419 patients of the Austrian 
MDS Study Group. Ann Oncol. 2010;21:114–9.
48. Breccia M, Federico V, Latagliata R, Mercanti C, D’Elia GM, Cannella L, 
et al. Evaluation of comorbidities at diagnosis predicts outcome in myelodysplastic 
syndrome patients. Leuk Res. 2011;35:159–62.
49. Loghavi S, Sui D, Wei P, Garcia-Manero G, Pierce S, Routhbort MJ, et al. 
Validation of the 2017 revision of the WHO chronic myelomonocytic leu-
kemia categories. Blood Adv. 2018;2:1807–16.