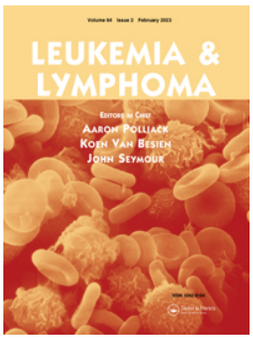

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ORIGINAL ARTICLE



# Adherence to quality indicators in chronic myeloid leukemia care: results from a population-based study in The Netherlands

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**ABSTRACT**

Suboptimal guideline adherence in chronic myeloid leukemia (CML) care is associated with worse treatment outcomes. Current study focused on adherence to seven quality indicators (QIs) based on the European Leukemia Network guideline (one diagnostic, one therapeutic, and five monitoring indicators). Data were obtained from population-based registries in the Netherlands of 405 newly diagnosed chronic phase CML patients between January 2008 and April 2013. Compliance rates regarding diagnostic and therapeutic indicator were 83% and 78%, respectively. Monitoring indicators rates were lower: 21–27% for indicators concerning the first year and 58% and 62% for the second and third year, respectively. Noncompliance occurred mostly due to non-timely monitoring. Twenty cases did not comply with any indicator, 6% complied with all indicators. After adjustment for age, overall survival rates did not differ significantly between the groups. Adherence to guideline-based QIs was suboptimal. This demonstrates the evidence-practice gap, shows room for improvement and underscores the need for real-world data.

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**KEYWORDS**
Chronic myeloid leukemia; CML; guideline adherence; response monitoring; survival

## Introduction

Before the introduction of the first tyrosine kinase inhibitor (TKI) imatinib in 2001, chronic myeloid leukemia (CML) was an often fatal disease, with allogeneic stem cell transplantation being the only curative treatment available. Treatment of CML has been revolutionized by the advent of TKIs, enabling most CML patients' life expectancy to approximate that of the general population [1–4].

Recommendations regarding CML care are established in various international guidelines; for example, the European LeukemiaNet (ELN) [5,6], and the US National Comprehensive Cancer Network (NCCN) [7]. These recommendations are based on clinical trials results, showing the excellent efficacy of TKIs. However, trial results may not be directly applicable to patients managed in routine clinical practice. Trials are characterized by a strict study protocol with precise endpoints where adherence is optimized and strictly monitored, follow-up schemes are highly protocolized, and more data are recorded than in routine clinical practice [8–11]. Most importantly, due to numerous exclusion criteria, the study population may not represent the general that typical CML population. Moreover, elderly patients are generally underrepresented in clinical trials [12,13]. Yet, nearly half of CML patients is aged 66 years and older and the population is growing due to the aging population [14]. Besides, patients who discontinued the study medication due to treatment failure or intolerance are often no longer included in further study follow-up.

The first step toward improving care is to gain insights into the quality of actual delivered care, for

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which real-world data are required [10]. Studies have shown that in real world, monitoring practices are not performed as rigorously as recommended in guidelines [15–18]. Patients who are adequately monitored have a significantly lower risk of progression when compared to suboptimal monitored patients [17,19,20]. Besides, TKI adherence, another crucial factor in CML management, is improved in patients receiving regular response monitoring [21]. Optimal monitoring reduces healthcare resource utilization and health care costs [22,23].

Previous studies of guideline adherence have focused on the frequency of monitoring, in part concerning specific moments in time (e.g. at 3, 6, or 12 months since the start of TKI). Investigating separate segments of the care process does not attain insights into the quality of the whole care process. Therefore, this study investigated the actual quality of care more broadly and tries to overcome the gap between evidence from guidelines and clinical practice using quality indicators (QIs). QIs have been defined as 'measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality of care' [24]. Ideally, QIs are derived from guideline-based recommendations and supplemented by expert clinical experience [25]. We developed a QI set based upon the ELN guideline describing the CML clinical pathway of diagnosis, treatment, frequency and timing of monitoring, and subsequent actions. Furthermore, we assessed to what extent was acted upon these QIs. Next, we assessed the relationship between adherence to QIs and overall survival (OS).

## Materials and methods

### Data sources and study population

All data, except for data on survival and molecular testing, were obtained from two population-based registries on CML patients in the Netherlands (PHAROS-CML and HemoBase). Combined, they provide data on all new CML patients aged ≥18 years in 75 of approximately 90 hospitals in the Netherlands, diagnosed between January 2008 and April 2013. Only patients diagnosed in chronic phase (CP) CML were included. Disease phase, Charlson Comorbidity Index, and risk scores (Sokal and EUTOS long-term survival score (ELTS)) were recorded per standard procedure [6,26–28]. Data concerning vital status and causes of death were retrieved from the nationwide Netherlands Cancer Registry and were available up to 1 February 2016. Data regarding molecular testing were obtained from all 15 molecular laboratories performing BCR-ABL1 diagnostic testing in the Netherlands. The study was conducted in accordance with the Declaration of Helsinki.

### Outcome measures

An expert panel of five professionals selected seven QIs (process indicators) based on the recommendations as provided by the ELN guidelines [6]. It encompassed one indicator for the process of diagnosing and classifying CML, one indicator for the initiation of treatment, and five indicators for the response monitoring (Table 1). During the selection process, the panel focused on indicators with crucial influence on CML care decisions. Indicators comprised a numerator (patients who received the care as recommended) and denominator (patients to whom care should be applied to). The outcome indicator consisted of OS in years since diagnosis.

Indicator 1 comprised the proportion of patients with molecular and cytogenetic testing at diagnosis, compared to all patients diagnosed with CML-CP. Indicator 2 comprised the proportion of patients with CML-CP prescribed a first-line TKI (i.e. imatinib, nilotinib, or dasatinib) within 28 days since diagnosis, compared to all CML-CP patients nationwide. The five

**Table 1.** Description of the indicators.

| | | |
|---|---|---|
| | *Diagnosis* | |
| Indicator 1 | % of patients with complete diagnostic molecular and cytogenetic workup at diagnosis | |
| | *Treatment* | |
| Indicator 2 | % patients receiving first-line TKI within 28 days after diagnosis. | |
| | *Follow-up* | |
| Indicators 3–7 | % Cytogenetic[a] and BCR-ABL (IS) monitoring at defined milestones and in case of milestone failure: | |
| | Performance of a mutation-analysis within 6 weeks | |
| | In presence of mutation: TKI switch | |
| | New BCR-ABL sampling within 2 months after failure | |
| | Indicator 3 | At 3 months ± 14 days |
| | Indicator 4 | At 6 months ± 14 days |
| | Indicator 5 | At 12 months ± 14 days |
| | Indicator 6 | At 24 months ± 60 days |
| | Indicator 7 | At 36 months ± 60 days |

TKI: tyrosine kinase inhibitor; IS: international scale.
[a]If a complete cytogenetic response (CCyR) was already achieved (and not lost) before the specific milestone, cytogenetic testing was marked as accomplished.

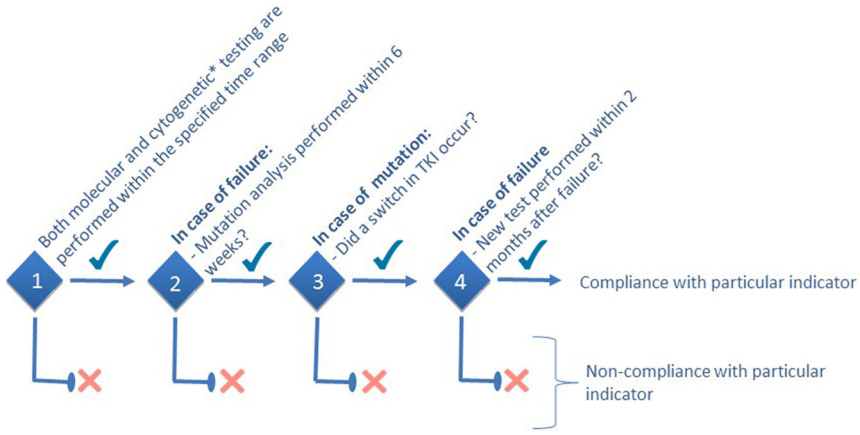


**Figure 1.** The four steps that comprise a follow-up indicator. At every step, cases are marked compliant of non-compliant. In case of noncompliance, the subsequent steps of that specific indicator cannot be further analyzed. *Cytogenetic testing was marked as accomplished when a complete cytogenetic response was already achieved (and not lost) before the next specific milestone.

monitoring indicators regarded the performance of monitoring tests at defined milestone time-points and the clinical actions when failing the targets according to ELN guidelines [29]. In case of milestone failure, compliance was also rated based on mutation analysis performance, TKI switch if a mutation was present, and performance of a new molecular test within 2 months after initial failure (Figure 1). In case of non-compliance to one of these steps, subsequent steps of that particular indicator were not further analyzed.

BCR-ABL1 transcripts values had to be reported on the international scale. Cytogenetic testing was marked as accomplished when a complete cytogenetic response was already achieved (and not lost) before the next specific milestone. The time range for mutation-analysis was established at 6 weeks after achieving a failed response, plus additional 10 days for the result to become available (i.e. 52 days). For the performance of a new molecular test, the range was 2 months plus seven days.

Indicators 3–7 matched the optimal monitoring process at 3, 6, 12, 24, and 36 months since the start of first-line TKI, respectively (Table 1). A maximum deviation of 14 days outside the intended date was allowed for the indicators in the first year, 60 days for indicators in the second and third year. An indicator outcome consisted of three categories: adherence, non-adherence, or information missing. When the range of a specified follow-up indicator exceeded the duration of treatment or follow-up in the database, cases for that indicator were excluded. Other exclusion criteria and eligible cases (i.e. denominator) were identified per individual indicator. Per patient, compliance with QIs was assessed, which resulted in an individual pathway (e.g. complied with indicator 1, 2, 5, and 6, noncompliance with indicators 3, 4, and 7). In addition, we also assessed the number of monitoring tests performed in the first year after starting treatment, regardless of the moment of testing within that year.

We categorized the following three combinations of QIs, referred to as patterns: diagnosis and monitoring (indicators 1 and 2), the first 12 months (indicators 1–5), and all indicators. In patterns, the denominator comprised the number of eligible cases of the indicator with the longest follow-up duration. For instance, regarding all indicators, the denominator is similar to the denominator of indicator 7.

### *Statistical methods*

Descriptive statistics were used for compliance rates to QIs. The Kaplan–Meier method with the log-rank test for trend was used to assess the relationship between suboptimal monitoring and survival. The Fine–Gray subdistribution hazard model was used in competing-risk analysis with death and disease progression as competing risks. A $p$ value $<0.05$ was considered significant. Pearson's or Spearman's correlation was used to test collinearity among independent variables, in case of strong correlation ($r > 0.6$), only the most clinically relevant variable was included. Multicollinearity was tested with the variance inflation factor. Analyses were performed using SPSS version 25 (IBM, Armonk, NY) and SAS software (SAS Institute Inc., Cary, NC).

## Results

The databases comprised 405 newly diagnosed patients with CP-CML between January 2008 and April

**Table 2.** Patient demographics at diagnosis.

| | Total ($n = 405$) | 0 indicator ($n = 30$) | 1–4 indicators ($n = 317$) | ≥4 indicators ($n = 58$) | $p$ value |
|---|---|---|---|---|---|
| Sex, *n* (%) | | | | | |
| Male | 223 (55) | 11 (5) | 182 (82) | 30 (13) | 0.079[c] |
| Female | 182 (45) | 19 (10) | 135 (74) | 28 (15) | |
| Treatment hospital, *n* (%) | | | | | |
| Academic | 96 (26) | 3 (3) | 62 (65) | 31 (32) | **<0.001**[c] |
| Nonacademic | 277 (74) | 22 (8) | 228 (82) | 27 (10) | |
| First-line treatment, *n* (%) | | | | | |
| Imatinib | 283 | 14 (5) | 232 (82) | 37 (13) | **0.017**[c] |
| Nilotinib | 61 | 6 (9) | 36 (59) | 19 (31) | |
| Dasatinib | 21 | 0 | 19 (90) | 2 (10) | |
| Interferon-alpha | 1 | 0 | 1 (100) | 0 | |
| Other | 1 | 0 | 1 (100) | 0 | |
| First-line TKI (generation), *n* (%) | | | | | |
| Imatinib | 283 (78) | 14 (5) | 232 (82) | 37 (13) | **0.013**[c] |
| 2GTKI | 82 (23) | 6 (7) | 55 (67) | 21 (26) | |
| Median (range) age at diagnosis (years) | 58 (43–69) | 69 (53–78) | 58 (44–69) | 49 (36–61) | **<0.001**[b] |
| Sokal risk score, *n* (%) | | | | | |
| Low | 93 (25) | 6 (7) | 71 (76) | 16 (17) | 0.821[c] |
| Intermediate | 169 (46) | 12 (7) | 132 (78) | 25 (15) | |
| High | 105 (29) | 10 (10) | 82 (78) | 13 (12) | |
| ELTS risk score, *n* (%) | | | | | |
| Low | 178 (49) | 11 (6) | 134 (75) | 33 (19) | 0.191[c] |
| Intermediate | 132 (36) | 10 (8) | 106 (80) | 16 (12) | |
| High | 57 (16) | 7 (12) | 45 (79) | 5 (9) | |
| Charlson Comorbidity Index[a], *n* (%) | | | | | |
| 0 | 126 (31) | 5 (4) | 95 (75) | 26 (21) | 0.064[c] |
| 1–2 | 134 (33) | 10 (7) | 104 (78) | 20 (15) | |
| 3–4 | 89 (22) | 8 (9) | 73 (82) | 8 (9) | |
| ≥5 | 56 (14) | 7 (13) | 45 (80) | 4 (7) | |

TKI tyrosine kinase inhibitor. 2GTKI second-generation tyrosine kinase inhibitor. ELTS: EUTOS long-term survival.
[a]Age adjusted. Two points for CML not included.
[b]Kruskal–Wallis test.
[c]Chi-square test.
$p$-value $<0.05$ considered statistically significant.

**Table 3.** Compliance rates.

| Indicator | *n/N* | (%) |
|---|---|---|
| 1 | 334/405 | (83) |
| 2 | 287/367 | (78) |
| 3 | 59/218 | (27) |
| 4 | 47/187 | (25) |
| 5 | 31/149 | (21) |
| 6 | 53/91 | (58) |
| 7 | 42/68 | (62) |

2013. Characteristics at diagnosis are summarized in Table 2. The majority was treated in a nonacademic hospital ($n = 277$; 68.4%), 55.1% ($n = 223$) were male, and the median age was 58 years (interquartile range 43–69). In the group that complied with ≥4 indicators, the median age at diagnosis was significantly lower and more patients were treated in academic hospitals and a smaller majority received imatinib. Compliance rates and reasons for noncompliance for each indicator are summarized in Table 3 and Supplemental Table 1, respectively.

### *Indicator 1 – diagnosis*

All patients in CP were included, regardless of therapy. In most cases ($n = 334$, 82.5%), both cytogenetic and molecular testing was performed at diagnosis. Testing was not performed in 7.7% and 9.9% of the cases, respectively.

### *Indicator 2 – therapy*

In 38 cases (9%), data concerning diagnosis were known, yet data regarding therapy were lacking. Therefore, we have excluded these cases in further analysis.

More than three quarters (287/367) received a first-line TKI within 28 days after diagnosis. In two cases, therapy was started in time, though it comprised other non-TKI therapy – i.e. interferon ($n = 1$) and hydroxyurea ($n = 1$). These cases were excluded from further analysis. In 78 cases, therapy was started outside the established time range.

### *Indicators 3–7 – follow-up*

Rates of compliance with indicators 3, 4, 5, 6, and 7 were 27.1%, 25.1%, 20.8%, 58.2%, and 61.8%, respectively (Table 3). Compliance rates specified to molecular testing only, i.e. when cytogenetic testing was not

taken into account, were 26.0%, 29%, 23.5%, 55.1%, and 55.0% for indicators 3–7, respectively.

In the case of noncompliance, failure to adhere to that particular indicator occurred mostly in the first step as illustrated in Figure 1; that is, due to lack of testing within the specified time range. Of all noncompliant cases, noncompliance occurred at the first step in 99.4%, 93.6%, 90.7%, 81.6%, and 92.3% for indicators 3, 4, 5, 6, and 7, respectively (Supplemental Table 1). Concerning the amount of tests performed, regardless of timing, during the first year since start treatment, 63% ($n = 210$) of the patient received three or more molecular tests, whereas 8% ($n = 28$) received none at all. For cytogenetic testing, these rates were 20% ($n = 67$) and 33% ($n = 111$). On average, three molecular and 1.4 cytogenetic tests were performed in the first 12 months since start treatment.

Among indicators 3–7, 31 cases were tested within the specified time range and achieved treatment response 'failure'. In 25 of these cases, mutation-analysis was never performed, in only one of the remaining six cases, analysis occurred within the range and the result was negative, the other five occurred after 52 days since milestone failure. Consequently, further analysis concerning TKI switches and more frequent monitoring could not be performed.

### QI patterns

Twenty cases did not comply with any indicator. At 36 months, 5.8% (4/68) complied with all seven indicators. The number of cases that complied with 1, 2, 3, 4, 5, or 6 indicators were 74, 165, 48, 31, 15, and 8, respectively. The diagnosis and treatment pattern (indicators 1 and 2) was complied with in the majority of cases (67.9%, 248/365), whereas a minority (9.4%, 14/149) complied with the first year pattern (indicators 1–5).

### Survival

The median survival follow-up of 405 CML-CP patients was 62.3 months (range 0.3–97.5). During follow-up, 74 patients died (18%) of whom 13 due to CML. For 365 CML-CP patients treated with first-line TKI, OS rates were 96% (95% CI: 94–98%), 90% (95% CI: 86–92%), and 84% (95% CI: 79–87%) after 1, 3, and 5 years since diagnosis, respectively. Taking the number of cases into account, grouping based on the number of compliant indicators was performed to allow for meaningful statistical analysis. Univariable analysis demonstrated that survival curves for groups based on the number of indicators complied with (none, 1–4, or ≥4) differed significantly ($p = 0.013$), as shown in Figure 2. For the group that complied to no indicator at all, 5-year OS was 80 (95% CI: 54–92%), for the group that complied to 1–4 indicators 82% (95% CI: 76–86%) and the group that complied to four or more indicators 95% (95% CI: 85–98%). However, in a multivariable Cox proportional hazards model with adjustment for sex, treatment hospital, therapy, and age at diagnosis, the effect of indicator lost statistical significance (Supplemental Table 2). Age at diagnosis was negatively associated with OS. No CML-related death occurred in the group that complied with 4–7 indicators, hence competing risk analysis comparing the three groups was not possible (Figure 3).

We compared the group that complied with at least one QI versus the group that complied with no QI at all, and found no significant difference ($p = 0.11$). When we adjusted the analysis for age, the difference remained non-significant ($p = 0.12$). Perhaps this could

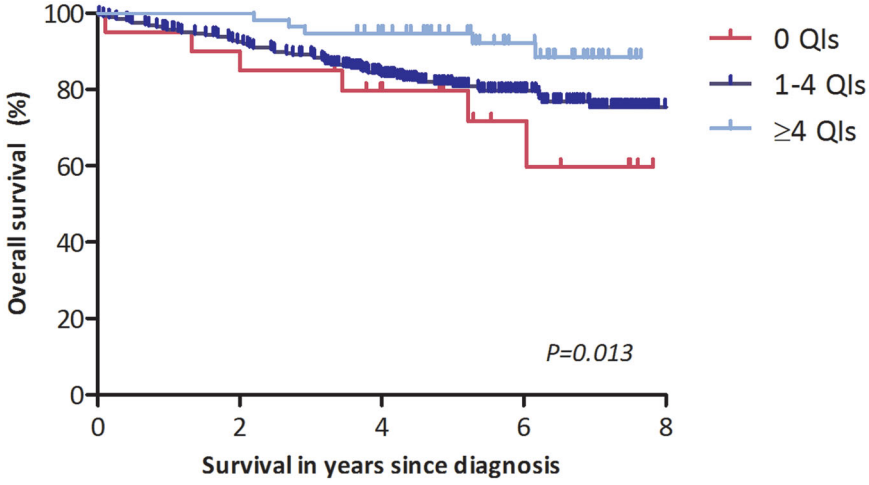


Figure 2. Survival curves for groups based on the amount of QIs (none, 1–4, and ≥4). QIs: quality indicators.

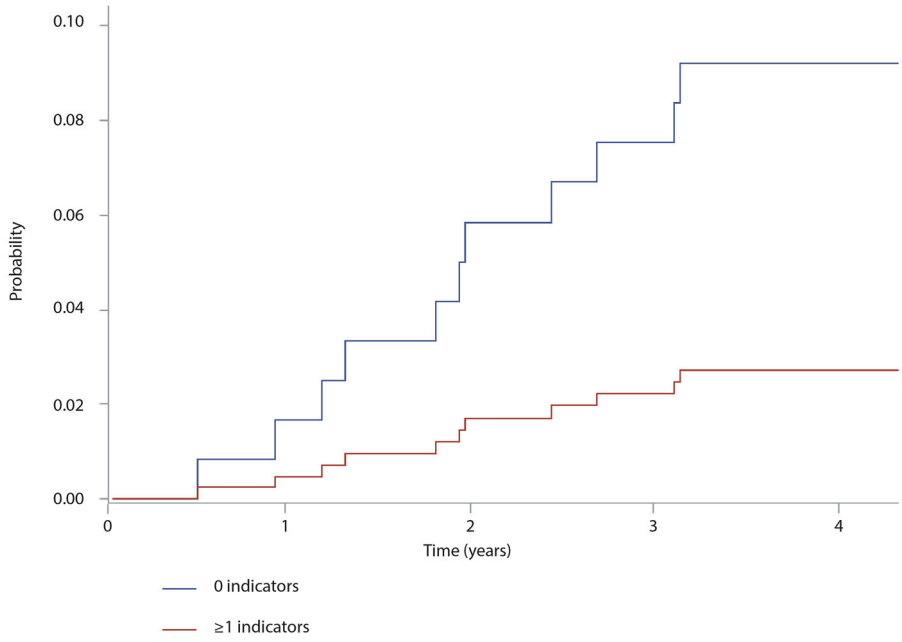


**Figure 3.** Competing risk survival analysis, with death and disease progression as competing risks, based on the amount of QIs (none versus ≥1). QIs: quality indicators.

be explained by the small amount of CML-related deaths.

## Discussion

This study shows that adherence to guideline-based process QIs in real-world clinical practice is lacking or not as strictly timed as in clinical studies. The number of cases that showed compliance to all indicators, i.e. concerning diagnosis, therapy, and monitoring, was staggeringly low (5.8%) when stringently assessed as prescribed by ELN guidelines, and 20 cases did not even comply with any indicator. In contrast to low compliance rates to monitoring indicators, most cases complied with both diagnostic and therapeutic indicators. The reason for noncompliance to monitoring indicators was due to a lack of testing within the specified time range in 81.6–99.4% of the non-compliant cases. When adjusted for age at diagnosis, survival rates did not differ significantly between cases that complied with no indicator, 1–4 indicators or ≥4 indicators.

Timely monitoring was a crucial factor in adherence to follow-up indicators. The lack of timely monitoring in this study illustrates the difficulty of translating recommendations as proposed by guidelines based on clinical studies directly into current practice. Further, it raises the question of whether the practical implications of the recommendations are feasible in current practice; that is, to plan appointments with the patient, collect blood samples, receive and act on the results and subsequently inform the patient, all in the specified time range.

Reported barriers to physician guideline adherence in the US include lack of familiarity, lack of time, resource barriers, lack of agreement, and inconvenience [30]. Furthermore, there appears to be a lack of interest among physicians in additional training or efforts to facilitate guideline adherence [30]. Organizational barriers could also contribute, which is suggested by the failure to monitor patients in a timely manner. We can only speculate on this remark, as related information was not included in our database. In our study, age at diagnosis in the group with the best compliance was significantly lower than in the other two groups, and overall, more than a third of the patients had moderate or severe comorbidity. One could speculate guideline deviation could have occurred deliberately in elderly patients, especially the ones with severe comorbidity, frailty or perhaps a limited life expectancy. It has already been reported that elderly patients in the Netherlands did not directly benefit from the advent of TKIs compared to younger CML patients, and that they experience excess mortality [2]. Perhaps this difference pertains not only to treatment initiation, but monitoring practices as well. Besides, comorbidities are the main cause of death for CML patients treated with TKIs [31], and in occurrence of another, more prominent, condition, physicians may be inclined to deviate from guidelines. As elderly and comorbid patients are often excluded from clinical trials [12,31], this challenge in clinical routine may not

be represented in the evidence-based guidelines. Our findings emphasize the need for real-world data concerning this subpopulation.

Perhaps the time range specified in our study was too narrow; however, a range of 28 days seems reasonable when testing should be performed every 3 months. Unfortunately, time ranges in other studies concerning guideline adherence are rarely specified. However, the importance of monitoring in a timely manner is illustrated by the change in the interpretation of treatment response if the day of collection of the 3-month sample was shifted by as little as five days [32]. The decline rate in BCR-ABL1 value is also predictive of treatment-free remission (TFR), which is becoming the ultimate goal of CML therapy [33]. In TFR, even more stringent monitoring is necessary to signal milestone loss and restart therapy [34].

Other studies support the finding that patients are rarely monitored in perfect accordance with the guidelines. For example, in community settings in the US, molecular monitoring was performed as recommended in only 39% of the patients, whereas 21% received no molecular testing in the first 18 months of treatment. For cytogenetic testing, the rates were 47% and 23%, respectively [18]. In another US study, at 12 months since start treatment, 23% of the patients underwent cytogenetic testing and 69% molecular testing. At 24 months, these rates were 12% and 54%, respectively [17]. In Canada, non-adherence to guideline recommendations at 12 months was reported in 20–30% of the patients [16]. Due to a variety in measurements of guideline adherence, the rates reported vary. However, when we disregard the exact timing of monitoring and focus on the frequency of molecular testing within the first 12 months since start treatment, a rough comparison can be made. Our study reports a higher rate of patients that received three or more molecular tests than the reported 27% in a study in the US [21]. In contrast, in the UK, a higher rate was reported of 86% [35].

European population-based studies concerning guideline adherence are scarce. Although monitoring was higher in Europe than in the US, they still confirm that recommendations on response monitoring have not been consistently translated in routine clinical practice [36]. In the Netherlands, a rate of adequate molecular response monitoring in the first year of TKI treatment of 74% was reported, based on the same data set as used by us now [15]. Adherence in this analysis was based on the frequency of molecular monitoring in the first 12 months, regardless of timing within this period, i.e. monitoring could have occurred four times within the first three months, without monitoring during the other months, and still be considered as compliant. Hence, these adherence rates are higher than presented in our study.

To close the evidence-practice gap, translation of study results into clinical practice by guidelines should be evaluated on the feasibility and subject to a quality improvement cycle [37]. After evaluating their application in real-world clinical practice, guidelines should be tailored to real-world clinical practice and vice versa [38]. Information regarding QIs is needed to develop tailored strategies to improve the quality of care.

Process QIs provide insights into the quality of the process and patients' clinical pathways over time [39]. For example, they enable comparisons between centers, regions, and time periods, among others. By showing the weak spots in current – real-world – care, they provide targets for quality improvement. To do so, more uniformity is required, in how we report, measure, and define guideline adherence. Likewise, standardization in QIs is required and a set of indicators should be validated in CML care. Next, their utilization should be optimized and incorporated in guidelines: per indicator cutoff values should be defined, as for quality goals and as a threshold for further clinical actions in case of noncompliance.

The same applies to the general outcome indicator, i.e. how we measure the effectivity of our guidelines. In this study, it encompassed survival. However, due to the improved survival rates, patients often die with their disease than because of it [31], and this outcome did not discriminate between the different pathways of compliance to the process indicators. Maybe the achievement of TFR would be a more suitable outcome.

Limitations of our study mainly pertain to the lack of information on reasons for noncompliance. To develop strategies aimed at guideline adherence improvement, barriers and facilitators to compliance should be explored. Few studies investigated barriers [30,40]; however, they are limited to US practices and do not focus on barriers to monitor patients promptly. To our knowledge, evaluation of guidelines in clinical practice with the aid of indicator patterns, i.e. individual patients' clinical pathways, is unique in CML care. The use of guideline-based QIs to investigate room for improvement of quality of care is well described in oncology care [41–45].

Unfortunately, we could not compare outcomes between the different care pathways a patient could experience because of the low compliance rates.

Future research should focus on improving the evaluation of the subsequent steps per follow-up indicator in case of failure and the pattern of seven indicators combined and adjust every QI to the newest guidelines [6].

In conclusion, our study with real-world data showed a lack of compliance with guideline-based process QIs. Real-world data concerning the subpopulations that are often excluded in clinical trials, such as elderly and patients with comorbidities, are called for. The lack of compliance offers room for improvement of clinical care and underscores the need for guidelines and their implementation tailored to real-life practice. To overcome this gap, we need a dynamic process of quality improvement in which compliance to process indicators can be used to evaluate the feasibility and subsequently adjust guidelines to clinical practice.

## Disclosure statement

The authors declare no competing interests.

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