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Changes in intensive care unit admission rates, organ support, and mortality in patients with acute myeloid leukaemia over a 12-year period: A Danish nationwide cohort study

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Abstract

Changes in acute myeloid leukaemia (AML) treatment may affect requirement for admission to and treatments in intensive care units (ICUs). We evaluated trends in ICU admission, use of organ support, and 1-year mortality in Danish AML patients. Of 1417 AML patients diagnosed 2005-2016, 28.0% (n=397) were ICU-admitted within 3 years, with no major change in admission rate during the 12-year period. Use of mechanical ventilation and dialysis decreased (66.7% to 40.6%), while use of non-invasive ventilation increased (20.0% to 50.0%). Concurrently, 1-year mortality declined among all patients (36.0% in 2005 to 28.8% in 2016) and ICU-admitted patients (80.0% to 65.6%).

Keywords

Acute myeloid leukaemia; intensive care; survival; population-based; organ support

The mortality of patients with acute myeloid leukaemia (AML) has decreased due to more aggressive treatment including extended use of allogeneic haematopoietic stem cell transplantation (HSCT)(1, 2). Although this has improved overall survival, increased treatment toxicity may affect early mortality and need for supportive therapy including intensive care unit (ICU) treatment. We evaluated trends in ICU admission rates, use of organ support, and 1-year mortality both overall and after ICU admission in Danish AML patients diagnosed from 2005 to 2016.

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The study included all adult AML patients registered in the Danish Acute Leukaemia Registry (DNLR)(3) diagnosed 2005-2016 and treated with high-intensity chemotherapy. Baseline patient, disease and treatment characteristics were obtained from the DNLR. Information on first ICU admission including use of mechanical ventilation (MV), non-invasive ventilation (NIV), dialysis or vasopressors after AML diagnosis was obtained from the Danish Intensive Care Database (DID)(4). Comorbidity and survival status information was obtained from the Danish National Patient Registry (DNRP)(5) and the Civil Registration System (CRP)(6), respectively. All data sources were linked on an individual level (Appendix Figure 1).

We examined rates of ICU admitted AML patients within 3 years of diagnosis. We calculated allogeneic HSCT rates, median time to first ICU-admission and HSCT. We examined the proportion of ICU admitted patients receiving organ supportive treatments during the first ICU admission after AML diagnosis as well as 1-year mortality after diagnosis and after ICU admission. Rates were compared by odds ratios estimated by mixed effects logistic regression, adjusted for potential confounders. We compared rates between 2013-2016 and 2009-2012 with 2005-2008 as reference. All analyses were conducted using StataIC version 15. The study was registered at the Danish Data Protection Agency. More details on data sources, methods and statistics can be found in appendix.

Overall, 1417 AML patients were included in the study. Within 3 years of diagnosis, 28.0% were admitted to an ICU with no major change in ICU admission rates from 2005-2008 to 2013-2016 (Table I). Median time to first ICU admission increased from 30 days (IQR 7-116) to 90 days (IQR 18-359) concurrently with HSCT transplantation rates (16.3% in 2005-2008 and 35.1 % in 2013-2016). Median time to transplantation remained stable (211 days (IQR 167 – 411)). Patient- and disease characteristics are presented in Appendix Table 1.

The median Simplified Acute Physiology Score (SAPS) II was 55 (IQR: 45-67) in patients diagnosed 2010-2012 and 52 (IQR: 44-62) in 2013-2016, suggesting no major change in severity of illness in ICU patients admitted after 2010. The use of MV decreased from 66.7% to 40.6% over the study period, with a parallel increase in the use of NIV from 20.0% to 50.0%. We found no major change in the overall use of ventilation. The use of dialysis and vasopressors decreased over the same time (Figure 1).

The 1-year mortality in the entire AML cohort decreased from 36.0% in 2005 to 28.8% in 2016. In ICU admitted patients (N=397), the 1-year mortality decreased from 80.0% to 65.6% (Figure 1). The comparison of adjusted rates within distinct periods is presented in Table I.

Over a 12-year period, more than one fourth of AML patients receiving high-intensity chemotherapy were admitted to an ICU within 3 years of diagnosis. Use of allogeneic HSCT increased over the study period with no major change in ICU admission rate. The use of MV, dialysis, and vasopressors decreased, while the use of NIV increased. Concurrently, the 1-year mortality declined for AML patients overall and in the subset of ICU admitted patients.

The mortality trends observed are in contrast to a recent large-scale American study(7) reporting decreased in-hospital mortality in AML patients overall (19.5% in 2004 to 14.5% in 2012), but constant in-hospital mortality for the ICU admitted subgroup. These differences may be explained by variations in European and American ICU usage and capacity(8, 9). In addition, we focused on patients receiving high-dose chemotherapy, while Halpern et al. included patients receiving palliative treatment. Assuming that palliative patients were rarely eligible for ICU admission, we excluded these from this study. Methodical issues concerning research of critical ill patients and treatment selection must be considered, when interpreting the results of this study(10). However, because of the stable ICU admission rate and SAPS II scores, we do not suspect a change in ICU selection strategy or disease severity at ICU admission, which could explain the decreasing ICU mortality.

Whether the observed changes in ICU treatment patterns contribute to the improved survival or to what degree the changes are a result of changes in ICU treatment strategy, treatment need, or both is less clear. For example, early initiation of invasive treatment e.g., in patients with severe kidney injury is not necessarily beneficial(11). As discussed in a review by Azoulay et al.(12) the use of non-invasive treatment can potentially prevent the need for invasive treatment, but on the other hand, invasive treatment can be lifesaving and should not be delayed in critical situations.

Allogeneic HSCT rates and time to first ICU admission increased concurrently. Allogeneic HSCT performance extends the period with risk of ICU admission due to immunosuppression, and treatment toxicity in addition to graft-versus-host disease(13). Allogeneic HSCTs reduce relapse risk and improve long-term survival in selected patients despite higher risk of treatment-related mortality(14). To what degree the increased transplant performance contributes to the observed improved 1-year mortality needs further investigation.

This nationwide study provides insight into 12-years of routine ICU-related clinical AML care. Our data offer complete follow-up and were collected independently from study aims limiting information bias. However, our analyses are limited by the number of ICU requiring patients, and the percentage of missing SAPS II score. National differences in health care systems, ICU capacity and ICU admission policies(8, 9), must be considered, but our findings are likely referable to countries with tax-supported health care systems across the world.

In conclusion, 1-year mortality for AML patients with and without ICU admission decreased from 2005 to 2016. Concurrently, ICU treatment patterns changed, with longer time to first ICU-admission, increased use of NIV treatment and decreased use of invasive treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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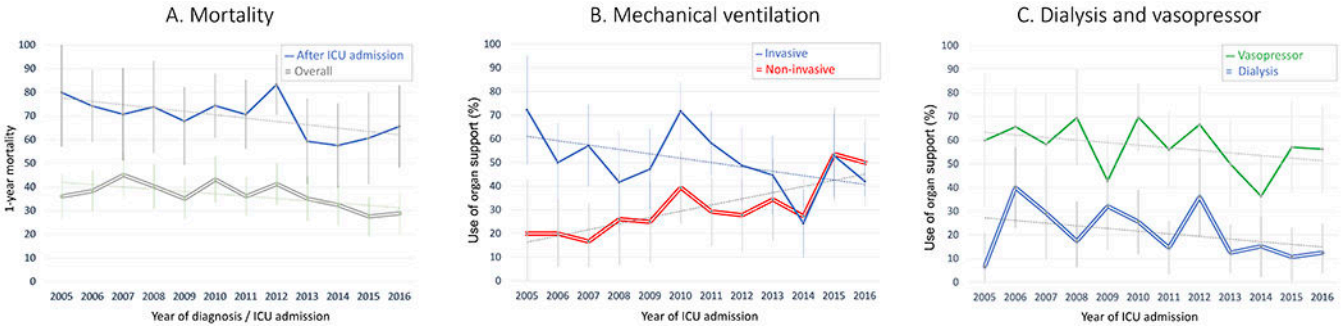

Figure I.

Changes in 1-mortality (A), use of mechanical ventilation (B) and use of dialysis and vasopressor (C). The graphs illustrate rates of either 1-year mortality or treatment and 95% confidence interval in the individual year. The dotted lines show a linear regression.

Table I.

Unadjusted and Adjusted Odds Ratios of Study Outcomes for AML patients

	Unadjusted OR (95% CI)					Adjusted OR (95% CI) *				
	2005-2008	2009-2012		2013-2016		2005-2008	2009-2012		2013-2016	
All AML patients			*p*		*p*			*p*		*p*
ICU admission	1.00 (ref.)	1.27 (0.96 – 1.70)	0.098	1.16 (0.86 - 1.55)	0.331	1.00 (ref.)	1.30 (0.97 – 1.73)	0.076	1.20 (0.89 - 1.61)	0.232
Death within 1 year of diagnosis’	1.00 (ref.)	0.92 (0.71 – 1.18)	0.513	0.63 (0.48 - 0.82)	0.001	1.00 (ref.)	0.84 (0.64 – 1.10)	0.211	0.57 (0.43 - 0.76)	<0.001
ICU admitted AML patients **										
Invasive mechanical ventilation	1.00 (ref.)	1.27 (0.76 – 2.11)	0.367	0.56 (0.33 - 0.94)	0.029	1.00 (ref.)	1.28 (0.86 – 1.89)	0.221	0.56 (0.37 - 0.84)	0.005
Non-invasive mechanical ventilation	1.00 (ref.)	1.76 (0.97 – 3.19)	0.065	2.83 (1.54 – 5.17)	0.001	1.00 (ref.)	1.73 (1.35 – 2.23)	<0.001	2.80 (1.41 - 5.53)	0.003
Any ventilation	1.00 (ref.)	1.27 (0.74 – 2.19)	0.388	0.82 (0.47 – 1.42)	0.481	1.00 (ref.)	1.21 (0.72 – 1.65)	0.470	0.80 (0.58 – 1.10)	0.174
Dialysis	1.00 (ref.)	0.98 (0.55 – 1.73)	0.947	0.41 (0.21 - 0.81)	0.010	1.00 (ref.)	1.00 (0.55 – 1.80)	0.998	0.42 (0.24 - 0.76)	0.004
Vasopressor	1.00 (ref.)	0.88 (0.57 – 1.37)	0.572	0.58 (0.45 - 0.74)	<0.001	1.00 (ref.)	0.88 (0.56 – 1.37)	0.572	0.58 (0.45 – 0.74)	<0.001
Death within 1 year of ICU	1.00 (ref.)	1.02 (0.57 – 1.82)	0.953	0.50 (0.28 – 0.89)	0.019	1.00 (ref.)	0.96 (0.53 – 1.73)	0.882	0.49 (0.19 – 1.31)	0.155

*Adjusted for age, sex, modified Charlson Comorbidity Index (mCCI, excluding acute leukemia-related comorbidity), type of AML (de novo, secondary or therapy-related) and accounting for clustering within ICU centers of the ICU admitted patients.

**ICU admission within 3 years of AML diagnosis.