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3

4 **Title**

5 **Clinical features of complex karyotype in newly diagnosed acute myeloid leukemia**

6

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51 **Abstract**

52 Complex karyotype acute myeloid leukemia (CK-AML) has been classified as
53 an adverse-risk subtype. Although a few reports have further classified CK-AML as
54 typical (including monosomy of chromosomes 5, 7 and 17 or deletion of 5q, 7q and/or
55 17p) or atypical, the clinical features of these subtypes in Japanese patients remain
56 unclear. We retrospectively analyzed a total of 115 patients with CK-AML, including
57 77 with typical CK-AML and 38 with atypical CK-AML. Median overall survival (OS)
58 was significantly shorter in patients with typical CK-AML than atypical CK-AML (143
59 days vs 369 days, $P=0.009$). Among patients with typical CK-AML, those with
60 monosomy 17 or deletion of 17p had significantly shorter OS than patients without such
61 abnormalities (105 days vs 165 days, $P=0.033$). *TP53* mutations were more
62 predominant in patients with typical CK-AML than in patients with atypical CK-AML
63 (69.7% vs 32.4%, $P < 0.001$). Patients with typical CK-AML had a poor prognosis
64 regardless of *TP53* mutation status. Among patients with atypical CK-AML, however,
65 prognosis was worse for those with the *TP53* mutation than those without the mutation.
66 In conclusion, prognosis is extremely poor for both typical CK-AML and atypical CK-
67 AML with *TP53* mutation.

68

69 **Keywords: Complex karyotype, CK-AML, Typical CK-AML, monosomy 17,**
70 **deletion of 17p, *TP53* mutation**

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87 **Introduction**

88 Acute myeloid leukemia (AML) is a remarkably heterogeneous disease
89 resulting from the acquisition of chromosomal rearrangements and multiple
90 genetic alterations [1-5]. Patients with AML who present with a complex karyotype
91 (CK) account for 10-12% of all AML patients [6-9]. CK-AML has been consistently
92 classified into an adverse risk group in international risk stratifications such as
93 European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN)
94 [10-14]. A few reports proposed that CK-AML can be further classified into typical
95 CK-AML and atypical CK-AML [15-17]. The former was defined as having CK
96 including monosomy of chromosomes 5, 7 and 17 or deletion of 5q, 7q and/or 17p, and
97 the latter was defined as having CK without those abnormalities. Although it has been
98 reported that patients with typical CK-AML have lower complete remission (CR) rates
99 and shorter overall survival (OS) than those with atypical CK-AML, the clinical
100 features of typical and atypical CK-AML remain unclear in Japanese cohort. Recently,
101 the presence of a pathogenic *TP53* mutation (at a variant allele frequency of at least
102 10%) defines a new entity of AML with mutated *TP53* [10, 18]. *TP53* mutation were
103 frequent in patients with CK-AML. Therefore, we analyzed clinical features of CK-
104 AML and the effects of chromosomal abnormalities and genetic alterations on
105 prognosis.

106

107 **Materials and Methods**

108 **Patients**

109 Hokkaido Leukemia Net (HLN) is a regional prospective cohort study
110 registering cases of newly diagnosed AML in Hokkaido, Japan (UMIN: 000048611).
111 We retrospectively analyzed AML cases except for acute promyelocytic leukemia
112 registered in HLN between April 2010 and December 2021. CK-AML were further
113 divided into typical CK-AML and atypical CK-AML. Survival curve was compared to
114 that of patients with normal karyotype (NK) AML. This study was conducted in
115 accordance with the Helsinki Declaration and was approved by the Hokkaido university
116 hospital institutional review boards (#015-0344).

117

118 **Definition of complex karyotype**

119 Definition of complex karyotype (CK) was based on the 2017 ELN
120 guidelines. More specifically, CK was defined as 3 or more chromosomal
121 abnormalities in the absence of the WHO-designated recurring translocations or

122 inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9),
123 inv(3) or t(3;3), and AML with *BCR-ABL1* [19].

124

125 **Analysis of genetic alterations**

126 Bone marrow (BM) or peripheral blood (PB) samples of 113 cases with CK-
127 AML were available for analysis of genetic alterations. We developed a compact AML
128 panel covering mutation hot spot of 14 genes including *TP53*, *CEBPA*, *NPM1*, *FLT3*,
129 *KIT*, *NRAS*, *KRAS*, *CBL*, *PTPN11*, *DNMT3A*, *IDH1*, *IDH2*, *RUNX1* and *ASXL1*. The
130 sequenced region for each gene is shown in supplemental table 1 (Table S1). Multiplex
131 polymerase chain reaction (PCR) products of genomic DNA were deep-sequenced at
132 Research Institute for Microbial Disease, Osaka University (Osaka, Japan) using Miseq
133 (Illumina, San Diego, CA). Only variants occurring with a variant allele frequency
134 (VAF) of more than 10% were defined as mutations.

135

136 **Statistical considerations**

137 Fisher's exact test was used to compare categorical values and the Mann-
138 Whitney U test was used to compare continuous values. Overall survival (OS) was
139 measured from the date of diagnosis until the date of death from any cause using the log
140 rank test. Statistical significance was defined as a two-tailed *P* value <0.05. The
141 following patients were considered in univariate analysis of determinants of overall
142 survival: patients who were 65 years or older, male gender, patients with typical CK-
143 AML, 5,000 or more WBC count at diagnosis, intensive chemotherapy, allogeneic-
144 hematopoietic stem cell transplantation (allo-HSCT), and *TP53* mutation. The factors
145 associated with at least borderline significance (*P*<0.10) in the univariate analysis were
146 subjected to multivariate analysis by Cox proportional hazard model. All statistical
147 analyses were performed with EZR ver 1.52 (Jichi Medical University Saitama Medical
148 Center), which is a graphical user interface for R (The R Foundation for Statistical
149 Computing, Vienna, Austria) [20].

150

151 **Results**

152 **Patient characteristics**

153 CK-AML patients (N=115) accounted for 13.8% and NK-AML patients
154 (N=345) accounted for 41.4% of the 834 non-APL AML patients. We compared the age
155 distributions and characteristics of patients with NK-AML and those with CK-AML
156 (Fig. S1, Table S2). In univariate analysis, patients with CK-AML were significantly

157 older with a lower white blood cell (WBC) count and lower percentage of BM blast
158 cells than those with NK-AML. Percentage of AML-MRC was higher in CK-AML
159 compared to NK-AML. Additionally, patients with CK-AML had a lower CR rate and a
160 higher primary induction failure (PIF) rate than those with NK-AML. The 115 CK-
161 AML cases included 77 typical CK-AML cases (67.0%) and 38 atypical CK-AML
162 cases (33.0%). We compared the characteristics of patients with typical CK-AML and
163 those with atypical CK-AML (Table 1). There were no significant differences between
164 patients with typical CK-AML and those with atypical CK-AML in a median age (68
165 years vs 66.5 years, $P=0.338$), WBC count at diagnosis ($3,600/\mu\text{L}$ vs $4,700/\mu\text{L}$,
166 $P=0.217$), percentage of BM blast cells at diagnosis (43.8% vs 58.4%, $P=0.106$), WT-1
167 levels in BM at diagnosis ($698.2 \times 10^{-4}/\text{K562}$ vs $282.5 \times 10^{-4}/\text{K562}$, $P=0.771$),
168 percentage of patients who received intensive chemotherapy (46.8% vs 63.2%,
169 $P=0.115$), and percentage of patients who received allo-HSCT (22% vs 26.3%,
170 $P=0.813$).

171

172 **Chromosomal abnormalities**

173 Patients with typical CK-AML had larger numbers of chromosome
174 abnormalities (median, 9 vs 4 abnormalities; $P<0.001$) and larger numbers of
175 monosomy (median, 3 vs 0 abnormalities; $P<0.001$) than those with atypical CK-AML.
176 The distribution of number of gains and losses (monosomy or deletion) of each
177 chromosomes in CK-AML is shown in Fig. 1A. Total events of monosomy or deletion
178 of autosomal chromosomes were greater than those of chromosomal gain in CK-AML
179 (total of 368 loss events vs 119 gain events). Patients with typical CK-AML had a larger
180 number of monosomy, deletion and/or gain events than did patients with atypical CK-
181 AML (median of 4 abnormalities per case vs 2 abnormalities per case, $P<0.001$) (Fig.
182 1B, C). In monosomy or deletion of chromosomes, abnormalities of chromosomes 5, 7
183 and 17 were the 3 most common events. In typical CK-AML patients, the numbers of
184 patients who had monosomy or deletion of chromosomes 5, 7 and 17 were 49, 39, and
185 28, respectively (Fig. 2).

186

187 **Prognostic analysis by chromosomal abnormalities**

188 Two-year OS rates in patients with typical CK-AML, patients with atypical
189 CK-AML and patients with NK-AML were 7.1%, 34.6% and 50.8%, respectively (Fig.
190 3). Median OS of patients with typical CK-AML was 143 days (95% CI: 106-183),
191 which was significantly shorter than that of patients with atypical CK-AML (median OS
192 of 369 days, 95% CI: 63-751, $P=0.009$) and that of patients with NK-AML (median OS

193 of 741 days, 95% CI: 565-932, $P=0.005$) (Fig. 3). There were no significant differences
 194 between patients with typical CK-AML and patients with atypical CK-AML in PIF
 195 (63.9% vs 50%, $P=0.301$), CR rate (55.6% vs 70.8%, $P=0.285$) and relapse rate (35% vs
 196 47.1%, $P=0.516$) in patients who received intensive chemotherapy (Table 1).

197 Within patients with typical CK-AML, there was no significant difference
 198 between OS for patients with monosomy 5 or deletion of 5q and OS for patients without
 199 such abnormalities (148 days vs 118 days, $P=0.694$) (Fig. 4A). OS for patients with
 200 monosomy 7 or deletion of 7q was also similar to that for patients without such
 201 abnormalities (148 days vs 142 days, $P=0.973$) (Fig. 4B). However, patients with
 202 monosomy 17 or deletion of 17p had a significantly shorter OS than that for patients
 203 without such abnormalities among patients with typical CK-AML (105 days vs 165
 204 days, $P=0.033$) (Fig. 4C). There were no significant differences between patients with
 205 monosomy 17 or deletion of 17p and patients without such abnormalities in PIF rate
 206 (54.5% vs 68%, $P=0.475$), CR rate (63.6% vs 52%, $P=0.718$) and relapse rate (42.9% vs
 207 30.8%, $P=0.651$). However, mortality rate within 1 month of patients with monosomy
 208 17 or deletion of 17p were significantly higher than patients without such abnormalities
 209 (20% vs 2.3%, $P=0.021$), excluding patients who received best supportive care. We
 210 compared patients with duplicative or triplicated chromosomal abnormalities including
 211 chromosomes 5, 7, and 17, and single chromosomal abnormalities, however there was
 212 no significant difference in OS (duplicated or triplicated deletion 148 days vs single
 213 deletion 127 days, $P=0.448$).

214

215 **Genetic alterations and prognostic analysis**

216 The most frequently mutated gene was *TP53*. *TP53* mutations were found in 65
 217 (57.5%) of the 113 patients with samples for analysis (Fig. 5). There were 50 patients
 218 with a single *TP53* mutation and 15 patients with a double *TP53* mutation. In 50
 219 patients with a single *TP53* mutation, 46 patients had single nucleotide substitution (45
 220 missense mutation, 1 splice acceptor variant), and 4 patients had short indels (3
 221 frameshift mutation, 1 in-frame mutation). Other gene mutations were less common:
 222 *IDH2* (N=5, 4.4%), *KRAS* (N=4, 3.5%), *FLT3* (N=4, 3.5%), *RUNX1* (N=4, 3.5%),
 223 *PTPN11* (N=3, 2.7%), *ASXL1* (N=3, 2.7%), *CBL* (N=2, 1.8%), *DNMT3A* (N=2, 1.8%),
 224 *KIT* (N=2, 1.8%), *NPM1* (N=2, 1.8%), *NRAS* (N=2, 1.8%), *CEBPA* (N=1, 0.9%) and
 225 *IDH1* (N=1, 0.9%) (Fig. S2). *TP53* mutations were more predominant in patients with
 226 typical CK-AML than in patients with atypical CK-AML (69.7% vs 32.4%, $P < 0.001$).
 227 The frequencies of other gene mutations were not significantly different between

228 patients with typical CK-AML and patients with atypical CK-AML (Table S3). Fifty-
 229 two patients (80%) had *TP53* mutation as a sole mutation.

230 In patients with CK-AML, 2-year OS rates in patients with *TP53* mutation and
 231 patients without *TP53* mutation were 12.3% and 21.8%, respectively. Median OS of
 232 patients with *TP53* mutation was 127 days (95% CI: 67-183), which was significantly
 233 shorter than that of patients without *TP53* mutation (median OS of 302 days, 95% CI:
 234 136-532, P=0.014) (Fig. 6A). A comparison of OS rates in patients with typical CK-
 235 AML and patients with atypical CK-AML with or without *TP53* mutation is shown in
 236 Fig. 6B. Median OS periods of typical CK-AML patients with *TP53* mutation, typical
 237 CK-AML patients without *TP53* mutation, atypical CK-AML patients with *TP53*
 238 mutation, and atypical CK-AML patients without *TP53* mutation were 139 days (95%
 239 CI: 72-183), 165 days (95% CI:111-481), 77.5 days (95% CI:20-408), and 574 days
 240 (95% CI:59-1119), respectively. Median OS in atypical CK-AML patients without
 241 *TP53* mutation was significantly longer than that in patients with *TP53* mutation
 242 (P=0.017). There were no significant differences between CK-AML patients with *TP53*
 243 mutation and CK-AML patients without *TP53* mutation in PIF rate (35.5% vs 47.4%,
 244 P=0.516), CR rate (56.7% vs 67.9%, P=0.427) and relapse rate (70% vs 46.4%,
 245 P=0.109). Patient characteristics of 4 subgroup defined by CK subtype and *TP53*
 246 mutation were shown on Table S4. In univariate analysis, age of 65 years or older, male
 247 gender, typical CK-AML, WBC count of 5,000 or more at diagnosis, intensive
 248 chemotherapy, allo-HSCT, and *TP53* mutation were significant factors for OS. In
 249 multivariate analysis, typical CK-AML (HR:1.727, 95% CI:1.015-2.940, P=0.044) and
 250 having received allo-HSCT were identified as significant risk factors for poor and
 251 favorable prognosis respectively in patients with CK-AML (Table 2).

252

253 Discussion

254 Although the risk categorization of AML has been updated frequently, CK-AML
 255 consistently corresponds to an adverse prognosis in NCCN and 2022 ELN risk
 256 classifications [10-12]. Besides CK-AML, monosomal karyotype, monosomy 5 or
 257 deletion of 5q, monosomy 7, monosomy 17, abnormalities of 17p, mutated *ASXL1*,
 258 *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1* or *ZESR2*, and mutated *TP53*
 259 also correspond to the adverse risk group in 2022 ELN [10].

260 CK-AML was classified into typical CK-AML and atypical CK-AML in a few
 261 reports [15-17]. Mrózek K, et al. reported the effects of chromosomal abnormalities and
 262 genetic alterations on prognosis in 96 patients with typical CK-AML and 40 patients
 263 with atypical CK-AML [15]. In their study, the percentage of typical CK-AML patients

264 with *TP53* mutation was larger than the percentage of atypical CK-AML patients with
265 *TP53* mutation (67% vs 10%, $P < 0.001$). Patients with typical CK-AML were older than
266 patients with atypical CK-AML (median age of 59 years vs 53 years, $P = 0.007$), and
267 patients with typical CK-AML had a lower WBC count (median count of 6,000/ μL vs
268 23,800/ μL , $P = 0.001$), lower percentage of BM blasts (46% vs 76%, $P < 0.001$), lower CR
269 rate (35% vs 59%, $P = 0.020$) and lower 3-year OS rate (1% vs 23%, $P < 0.001$) than those
270 in patients with atypical CK-AML. Leung G, et al. also reported that the leukemia-free
271 survival (LFS) period was significantly shorter in typical CK-AML patients with *TP53*
272 mutation than in atypical CK-AML patients without *TP53* mutation (median LFS, 0.50
273 years vs 1.73 years, $P = 0.008$) [16]. In our analysis, patients with typical CK-AML had
274 a worse OS than that of patients with atypical CK-AML. However, there were not
275 significant differences in age, WBC count, percentage of BM blasts at diagnosis, CR
276 rate and PIF rate between patients with typical CK-AML and those with atypical CK-
277 AML (Table 1). Although a panel sequence is not currently available as daily practice in
278 Japan, typical CK-AML is defined just by chromosomal analysis and is identified as
279 poorer prognostic group within CK-AML in our analysis.

280 The pathogenesis of typical CK-AML is currently unclear [21]. In our analysis
281 of gain and monosomy or deletion of each chromosome, patients with typical CK-AML
282 had more monosomy, deletion and/or gain abnormalities than did patients with atypical
283 CK-AML. In monosomy or deletion of autosomal chromosomes, abnormalities of 5, 7
284 and 17, which belong to typical CK-AML, were the most common. Monosomy 17 or
285 deletion of 17p, which affects the *TP53* gene locus (17p.31), results in loss of
286 heterozygosity and a complete disruption of p53 function [17]. Monosomy 17, but not
287 monosomy 5 and/or 7, was associated with inferior OS among patients with CK-AML
288 [22]. In our cohort, we can also confirmed that the patients with monosomy 17 or
289 deletion of 17p had significantly shorter OS than that of other typical CK-AML
290 patients.

291 In our gene analysis, CK-AML patients with *TP53* mutation had a worse
292 prognosis than that of patients without *TP53* mutation. However, typical CK-AML
293 patients, especially those with monosomy 17 or deletion of 17p, had poor prognosis
294 regardless of *TP53* mutation. Mutations of *TP53* have been shown to be associated with
295 genomic instability, rapid gain or loss of chromosomes, and expression of various genes
296 to maintain genomic stability, mitosis and transcriptional regulation [16]. Abnormalities
297 of chromosome 17, where the *TP53* gene locus resides, contribute to poor prognosis,
298 and loss of genes on 17q such as *ERBB2*, *NF1*, *RARA*, *BRC1*, and *STAT3* might also
299 contribute to poor prognosis [22]. These abnormalities of genes would have been

300 responsible for the poor prognosis of CK-AML with monosomy 17 or deletion of 17p in
301 our cohort. *TP53* is the sole mutated gene in up to 75% of CK-AML patients with *TP53*
302 mutation, while 25% of the patients have co-occurring mutations including *FLT3*,
303 *NPM1*, *IDH1*, *IDH2*, *DNMT3A*, *WT1*, *RUNX1* and *RAS* mutations [23-28]. Gene
304 analysis in our cohort showed that 52 patients (80%) had *TP53* mutation alone.

305 The current study has several limitations. First, this study was a study with a
306 small number of patients and was retrospective in nature. A larger cohort is needed to
307 evaluate the effects of chromosomal abnormalities and genetic alterations on prognosis
308 of CK-AML. Second, we did not evaluate more patients who received VEN plus AZA
309 in detail, although VEN in combination with conventional low-intensity drugs is an
310 effective therapy for older AML patients [29]. VEN plus AZA may affect the prognosis
311 of CK-AML. We should plan to accumulate more cases in the future. Recently, APR-
312 246, which is a methylated PRIMA-1 analogue, has been reported to be one of the most
313 promising agents for patients with *TP53* mutation. APR-246 restores wild-type p53
314 conformation and activity. As a result, APR-246 induces prompt apoptosis in *TP53*
315 mutated cells. This drug in combination with traditional chemotherapeutic agents has a
316 synergistic effect [30-32]. The prognosis of typical CK-AML and atypical CK-AML
317 with *TP53* mutation might be improved by developing *TP53*-targeted therapy.

318 In conclusion, this retrospective analysis showed that the poor prognosis group
319 of CK-AML could be further stratified into typical CK-AML and atypical CK-AML.
320 Patients with typical CK-AML had a worse prognosis than that for patients with
321 atypical CK-AML in a Japanese cohort. Patients with monosomy 17 or deletion of 17p
322 had significantly shorter OS than that for other typical CK-AML patients. In gene
323 analysis, patients with *TP53* mutation had a worse prognosis than that for patients
324 without *TP53* mutation in CK-AML. However, typical CK-AML patients had poor
325 prognosis regardless of *TP53* mutation. This extremely poor prognostic group of CK-
326 AML patients with monosomy 17 or deletion of 17p can be identified before genetic
327 testing and long survival has not been achieved by current treatments.

328

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334

335 **Author contributions**

336 S.Y. and M.O. designed the study, analyzed the data and wrote the manuscript.
 337 T. K. provided critique to the manuscript. T.T. revised and approved the manuscript. All
 338 authors contributed to the final version of the manuscript and approved it for the
 339 publication.

340

341 **Disclosure of conflict of interest**

342 The authors declare no competing conflict of interest.

343

344 **Figure legends**

345 **Fig. 1.** Distributions of number of gains and losses (monosomy or deletion) of
 346 chromosomes. A. total CK-AML, B. typical CK-AML, C. atypical CK-AML. The
 347 upper half of the axis is gain events of chromosomes (red line) and the lower half is loss
 348 events of these chromosomes (black and pink lines). The pink line shows the number of
 349 cases with $-5/\text{del}(5q)$, $-7/\text{del}(7q)$ and/or $-17/\text{del}(17p)$, which is a hallmark of typical CK.
 350 Each autosomal chromosomal abnormality is shown in order of number of the
 351 chromosome from the left, and X and Y chromosomes are shown next to chromosome
 352 22.

353

354 **Fig. 2.** From top to bottom, numbers of typical CK-AML cases including $-17/\text{del}(17p)$, $-$
 355 $7/\text{del}(7q)$ and $-5/\text{del}(5q)$ are shown. Each column represents a case showing a
 356 combination of affected chromosomes.

357

358 **Fig. 3.** Overall survival rates of patients with typical CK-AML, patients with atypical
 359 CK-AML and patients with NK-AML are shown by red, black, and green lines,
 360 respectively.

361

362 **Fig. 4.** Overall survival rates of patients with typical CK-AML stratified by type of
 363 chromosomal abnormalities are shown (A. Comparison by whether or not $-5/\text{del}(5q)$
 364 was included, B. Comparison by whether or not $-7/\text{del}(7q)$ was included, C.
 365 Comparison by whether or not $-17/\text{del}(17q)$ was included).

366

367 **Fig. 5.** Relationships between type of chromosome abnormalities and 14 gene mutations
 368 are shown. From top to bottom, 14 genes are shown in descending frequency order.
 369 Rows show cases of typical CK-AML with $-17/\text{del}(17p)$, typical CK-AML without $-$
 370 $17/\text{del}(17p)$, and atypical CK-AML.

371

372 **Fig. 6. A.** Overall survival rates of CK-AML patients with *TP53* mutation and CK-
 373 AML patients without *TP53* mutation are shown. **B.** Overall survival rates of typical
 374 CK-AML patients with *TP53* mutation, typical CK-AML patients without *TP53*
 375 mutation, atypical CK-AML patients with *TP53* mutation, and atypical CK-AML
 376 patients without *TP53* mutation are shown by black, red, green, and blue lines,
 377 respectively.

378

379 **Table 1. Comparison of the characteristics of patients with typical CK-AML and**
 380 **patients with atypical CK-AML**

381

382 **Table 2. Univariate and multivariate analyses of patient characteristics for overall**
 383 **survival**

384

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Fig. 1

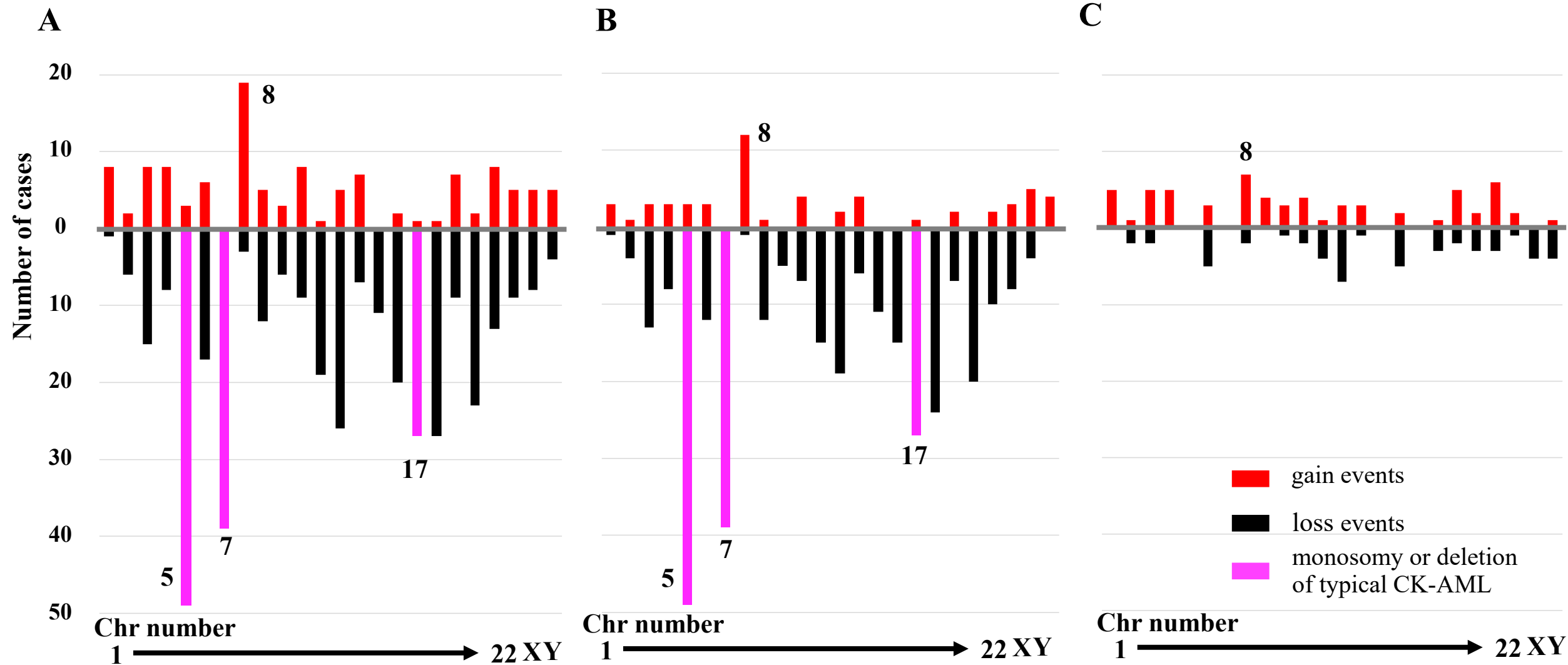


Fig. 2

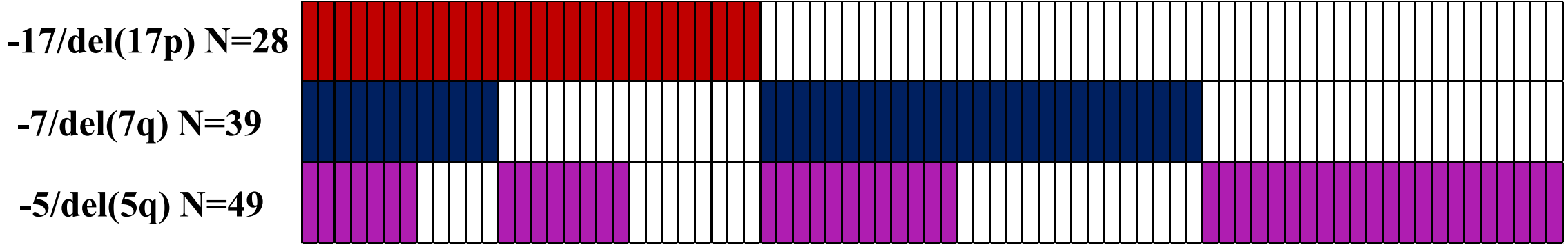


Fig. 3

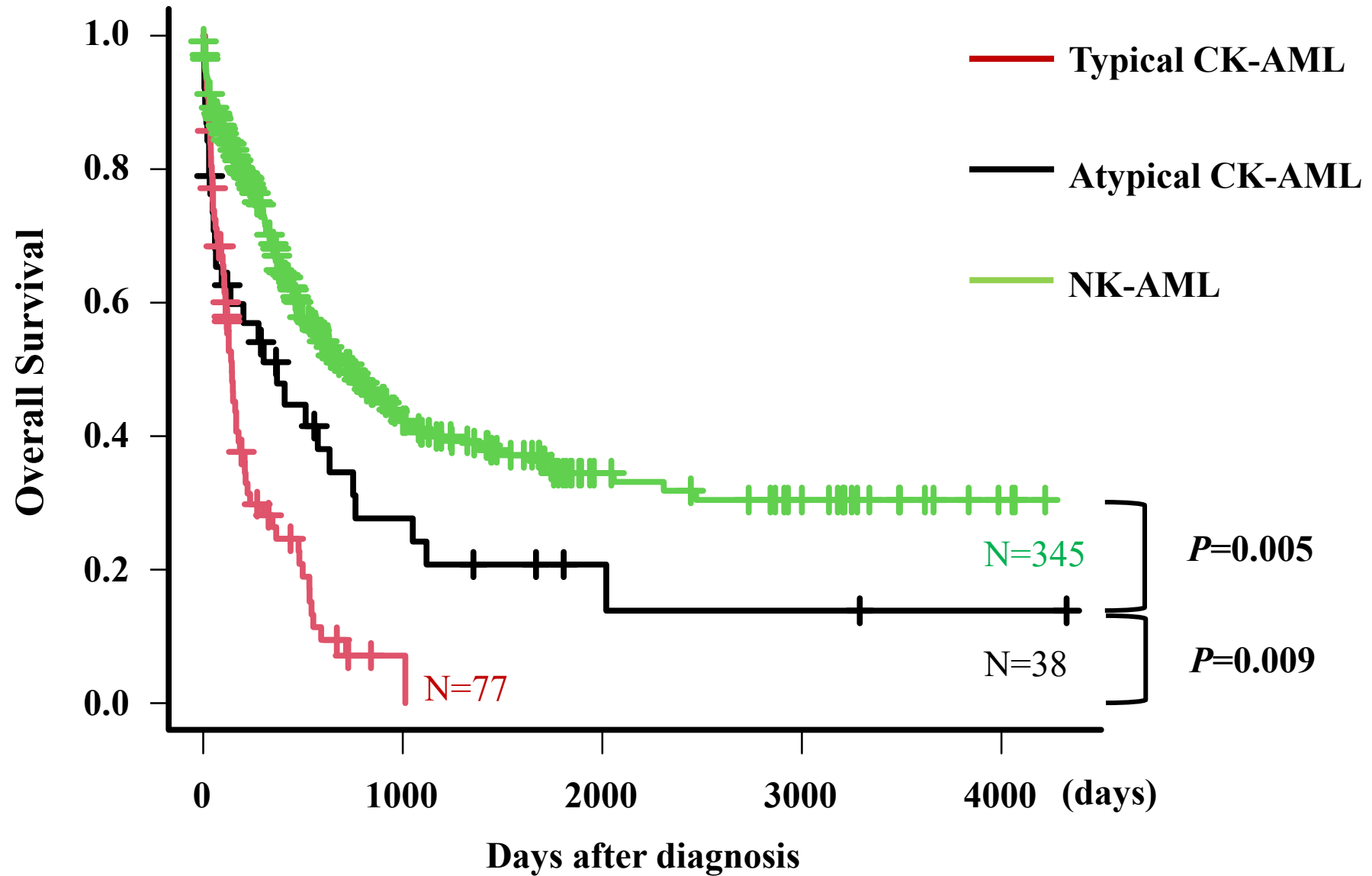


Fig. 4

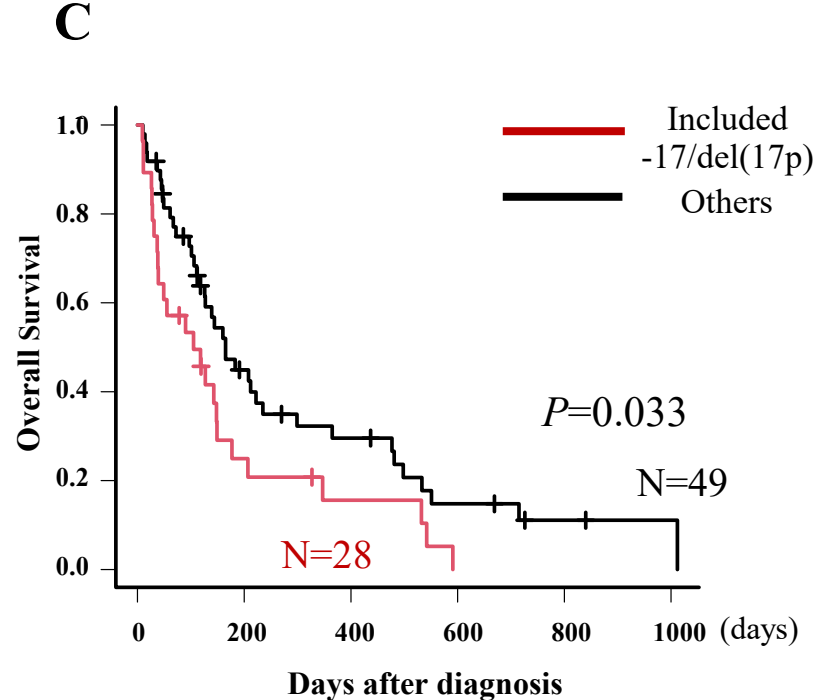
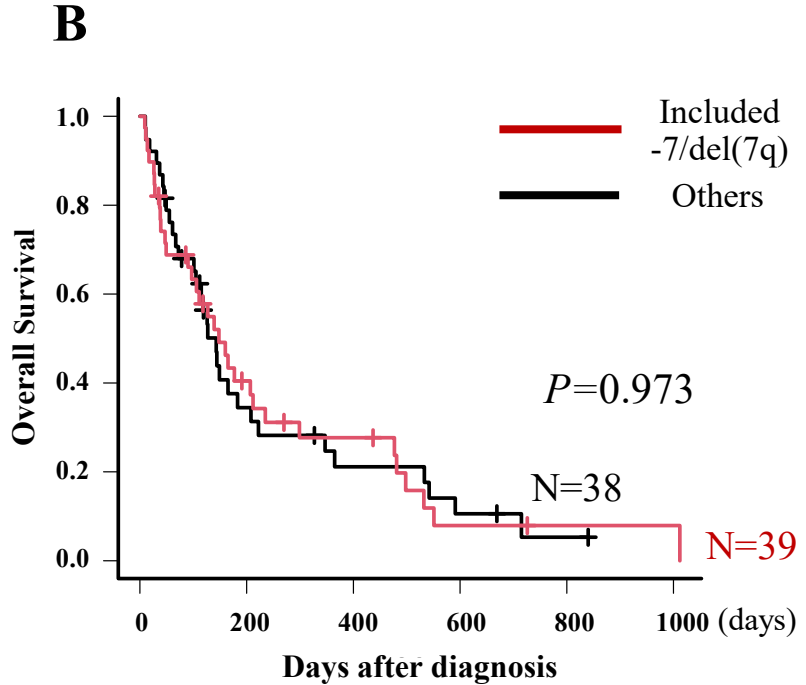
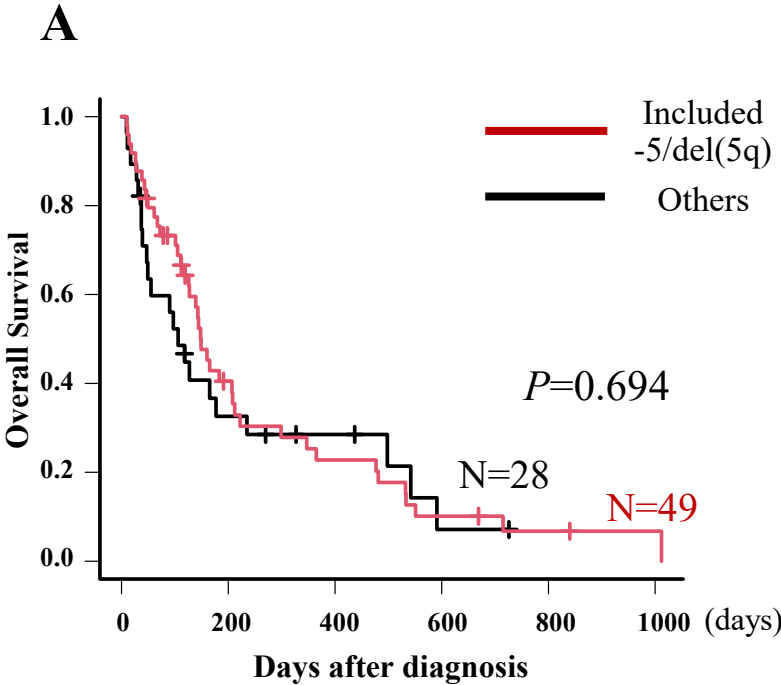


Fig. 6

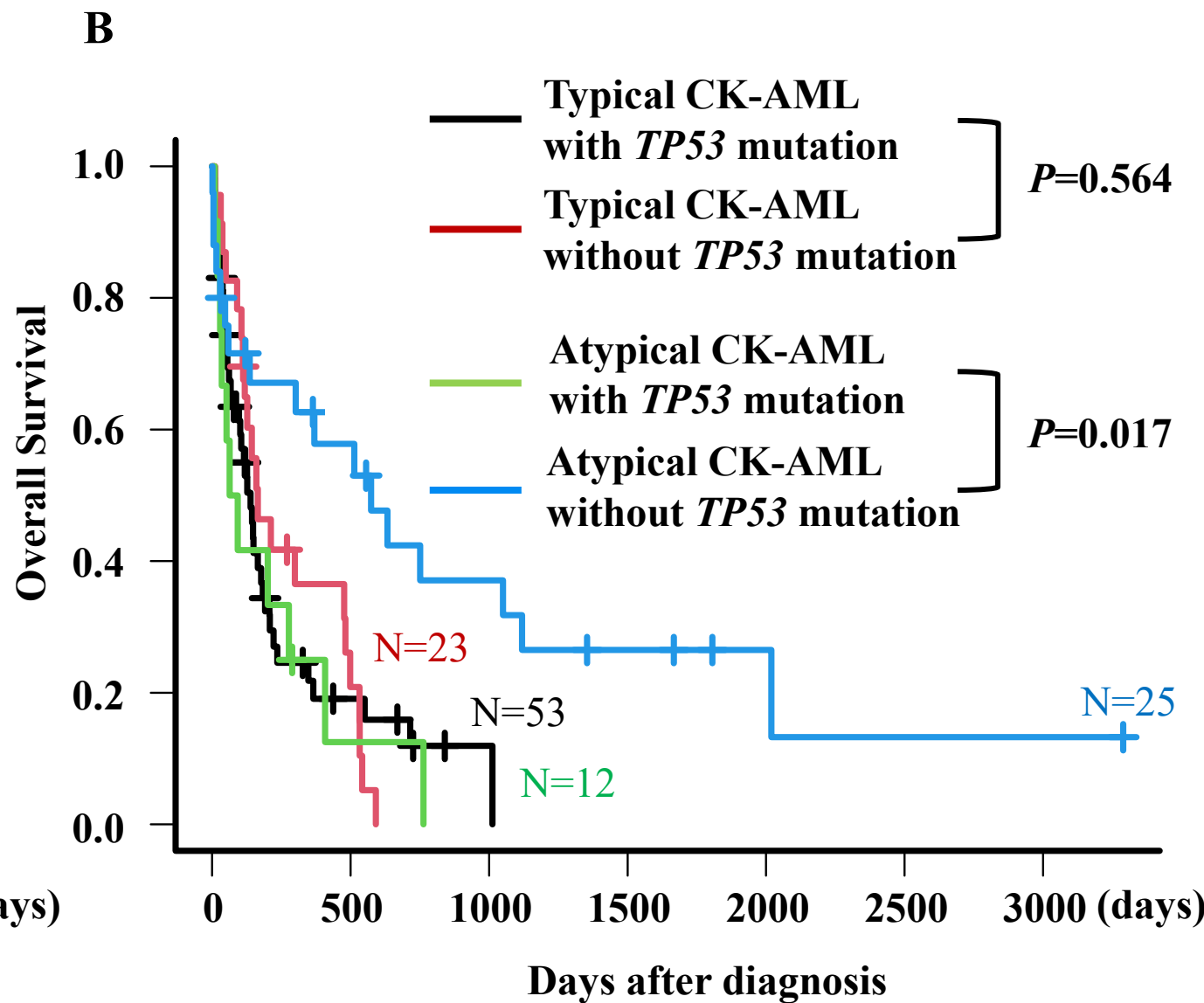
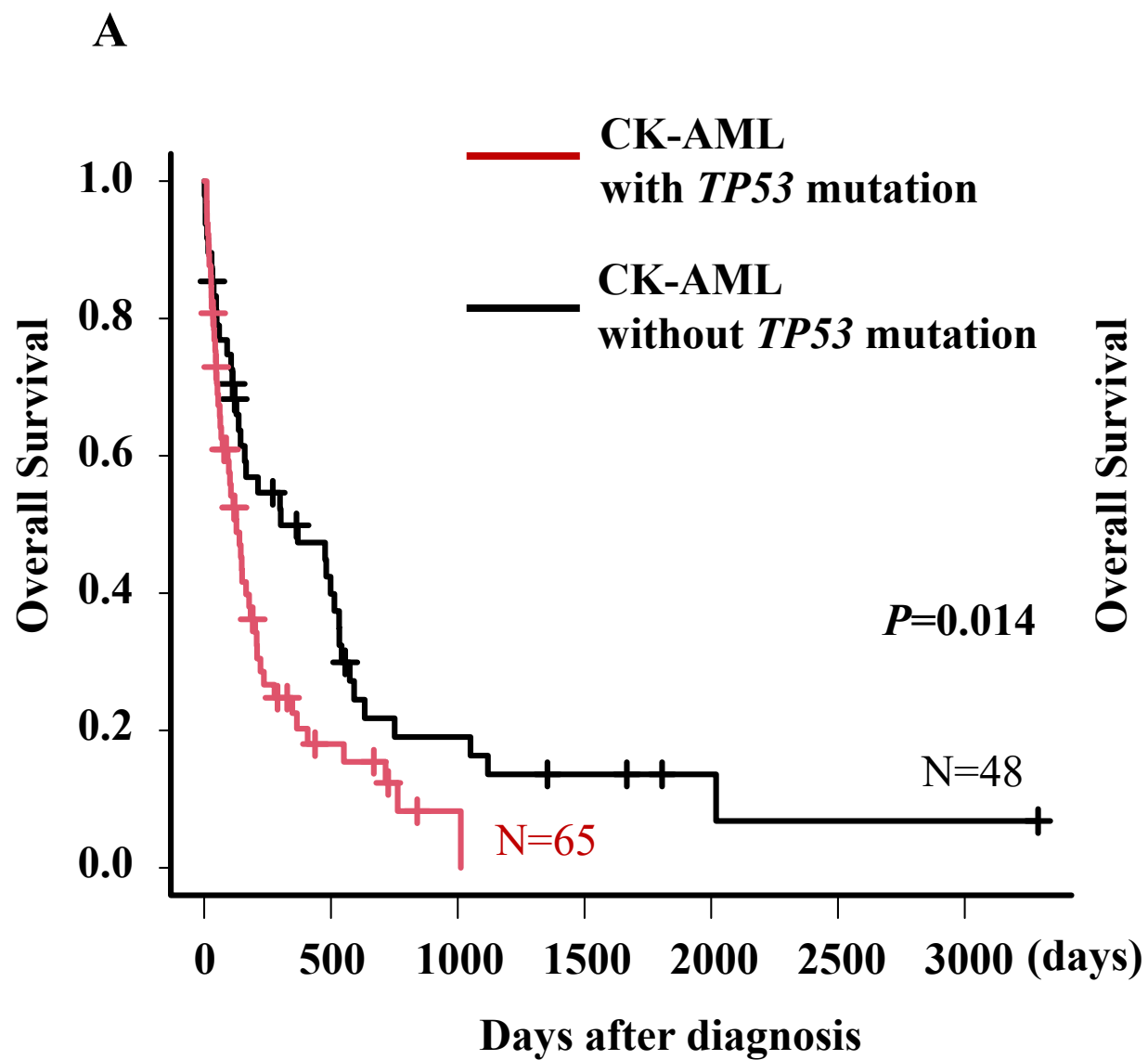


Table 1. Comparison of the characteristics of patients with typical CK-AML and patients with atypical CK-AML

	Typical CK-AML (N=77)	Atypical CK-AML (N=38)	<i>P</i> value
Median age [range]	68 [17-91]	66.5 [32-89]	0.338
65 years or older	50 (64.9%)	23 (60.5%)	0.684
Gender			
Male/Female	46/31	23/15	1
Disease			
AML-MRC	72(93.5%)	35 (92.1%)	1
t-AML	5 (6.5%)	2 (5.3%)	1
Myeloid sarcoma	0	1 (2.6%)	0.330
WBC (/μL) [range]	3,600 [700-85,800]	4,700 [700-117,000]	0.217
BM blast (%) [range]	43.8 [20-95]	58.4 [21-98]	0.106
BM WT-1 levels (x 10⁻⁴/K562) [range]	698.2 [1-6,441.7]	282.5 [1-4,764.3]	0.771
Number of chromosome abnormalities (/case)	9 [3-17]	4 [3-20]	<0.001
Number of monosomy (/case)	3 [0-10]	0 [0-6]	<0.001
Induction regimen			
Intensive chemotherapy*	36 (46.8%)	24 (63.2%)	0.115
VEN+AZA	7 (9.1%)	1 (2.6%)	0.268
AZA	10 (13%)	2 (5.3%)	0.332
CAG	14 (18.2%)	7 (18.4%)	1
Others	2 (2.5%)	3 (7.9%)	0.330
BSC	8 (10.4%)	1 (2.6%)	0.268
Allo-HSCT	17 (22%)	10 (26.3%)	0.813
PIF[†]	23 (63.9%)	12 (50%)	0.301
Achieve CR[†]	20 (55.6%)	17 (70.8%)	0.285
Relapse[†]	7 (35%)	8 (47.1%)	0.516
Cause of death			
AML	37 (59.7%)	16 (59.3%)	1
Infection	15 (24.2%)	6 (22.2%)	1
TRM	4 (6.4%)	1 (3.7%)	1
Others	6 (9.7%)	4 (14.8%)	1

Allo-HSCT: allogeneic-hematopoietic stem cell transplantation, AML: acute myeloid leukemia, AML-MRC: AML with myelodysplasia-related changes, AZA: azacytidine, BM: bone marrow, BSC: best supportive care, CAG: low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor, CK: complex karyotype, CR: complete response, PIF: primary induction failure, t-AML: therapy related AML, TRM: treatment-related mortality, VEN: venetoclax, WT-1: Wilms tumor-1 gene

*Intensive chemotherapy composed of anthracyclines and cytarabine

†PIF, Achieve CR, and Relapse were calculated for those who treated by intensive chemotherapy.

Table 2. Univariate and multivariate analyses of patient characteristics for overall survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
65 years or older	1.775 (63-165)	0.011	0.720 (0.370-1.398)	0.332
Male gender	1.657(1.078-2.547)	0.021	1.470 (0.941-2.295)	0.090
Typical CK-AML	1.895 (1.169-3.073)	0.010	1.727 (1.015-2.940)	0.044
5,000 or more WBC count at diagnosis	1.210 (0.792-1.849)	0.377	–	
Intensive chemotherapy*	0.564 (0.371-0.858)	0.007	0.957 (0.552-1.656)	0.876
Allo-HSCT	0.342 (0.200-0.583)	<0.001	0.267 (0.125-0.573)	<0.001
<i>TP53</i> mutation	1.718 (1.108-2.663)	0.016	1.459 (0.908-2.345)	0.119

Allo-HSCT: allogeneic-hematopoietic stem cell transplantation, AML: acute myeloid leukemia, CK: complex karyotype

*Intensive chemotherapy composed of anthracyclines and cytarabine