

# Social deprivation independently impacts clinical outcomes in patients with chronic lymphocytic leukemia

Data from the Surveillance, Epidemiology, and End Results (SEER) database shows that chronic lymphocytic leukemia (CLL) patients with higher social economic status have better outcomes but the reasons underlying this observation remain undetermined.<sup>1</sup>

This single center study (ethical approval granted by South East Wales Research Ethics Committee -02/4806) of 665 prospectively diagnosed participants between August 2005 and December 2019 i.e., prior to the Covid-19 pandemic, included 413 (62.1%) males and 252 (37.9%) females who were overwhelmingly white Caucasian (98%). There were two (2005-2010) and then a single specialist consultant (2010-2019) managing primary, secondary and tertiary patients through two specialist CLL clinics. Patients were diagnosed according to the five-parameter immunophenotyping scoring system.<sup>2</sup> Prognostic markers included clinical stage, lymphocyte doubling time (LDT), CD38 expression,  $\beta$ -2 microtubulin (B2M), immunoglobulin heavy-chain gene variable region (IGHV) mutation status at diagnosis with cytogenetic analysis (fluorescence *in situ* hybridization) routinely performed prior to treatment initiation. Patients were managed in accordance with the prevailing national/international guidelines with all eligible patients offered access to all licensed drugs and various open clinical trials, *Online Supplementary Table S1*.<sup>3</sup> The Welsh Government's Welsh Index of Multiple Deprivation (WIMD - last update 2019) provides a weighted (%) relative deprivation scoring system derived from eight domains - income (22%), employment (22%), health (15%), education (14%), access to services (10%), housing (7%), community safety (5%) and physical environment (5%), <https://www.gov.wales/sites/default/files/statistics-and-research/2020-06/welsh-index-multiple-deprivation-2019-results-report.pdf> - providing each individual household with a deprivation score. Patients were assigned into categories of relative deprivation based on quartiles with Cox regression for univariate and multivariable analyses used for primary outcomes, Pearson's  $\chi^2$  for relative deprivation and prognostic markers and Mann-Whitney U test for age. Analysis was conducted in Stata version 17. The Kaplan-Meier plots were generated using R version 4.2.1. The median age at diagnosis was 67 years with the overwhelming majority of patients (87.3%) presenting with early-stage disease (stage A/A0) and good prognostic markers: lymphocyte doubling time (LDT) >12 months (85.7%), low CD38 expression (66.7%), low B2M (70.7%), mutated IGHV genes (70.1%) and no adverse cytogenetics (78.9%), Table 1. In keeping with the published literature, age, stage, LDT, CD38, IGHV status and B2M at diagnosis were all identified as poor prognostic markers as was adverse cytogenetics (11q and/or 17p deletions). The likelihood of a poorer outcome was predicted

by level of deprivation independently and after adjusting for other explanatory covariates, *Online Supplementary Table S1*. There was significantly better overall survival with the least deprived having improved survival compared to the most deprived group (2<sup>nd</sup> most deprived hazard ratio [HR]=0.85, 95% confidence interval [CI]: 0.59-1.25,  $P=0.413$ ; 2<sup>nd</sup> least deprived HR=0.8, 95% CI: 0.52-1.22,  $P=0.294$ ; least deprived HR=0.59, 95% CI: 0.42-0.82,  $P=0.002$ ), Figure 1.

Progression-free survival (PFS) and time-to-first treatment (TTFT) showed no statistically significant difference between the various deprivation quartiles ( $P=0.084$  and  $P=0.23$ , respectively) and the most deprived *versus* the least deprived quartile ( $P=0.087$  and  $P=0.236$ , respectively). However, analyzing just those patients requiring treatment, survival from the time of first treatment, was significantly worse in the more deprived when comparing the four quartiles ( $P<0.001$ ), Figure 2.

The overall cohort had a median age at diagnosis of 67 years, but those with advanced-stage disease (stages B or C) presented at a significantly earlier age (60 vs. 67 years,  $P<0.001$ ), *Online Supplementary Table S2*. Although there was no substantial difference in age at diagnosis for patients presenting with early-stage disease (65 vs. 67 years - most vs. least deprived,  $P=0.153$ ) across deprivation quartiles, the least deprived group with advanced-stage disease presented 10 years younger (57 vs. 67 years;  $P=0.074$ ), *Online Supplementary Table S2*. Interestingly, the age at diagnosis for the most deprived is almost identical whether they presented with early- or advanced-stage disease (65 vs. 67 years,  $P=0.835$ ) whereas there was a significant 10-year difference in the least deprived quartile (67 vs. 57 years,  $P=<0.001$ ), *Online Supplementary Table S2*. On average, the most deprived patients presenting with advanced-stage disease showed a median survival of 10.5 years from diagnosis whereas the least deprived lived 15 years, *Online Supplementary Table S2*.

Analyzing only the 263 patients who died, as expected advanced-stage disease was associated with significantly earlier death (81 vs. 71 years,  $P<0.001$ ) with earlier death also associated with increasing deprivation ( $P=0.052$ ). The most deprived quartile early-stage patients died 1.5 years earlier ( $P=0.077$ ) but the age of death for advanced-stage disease was similar ( $P=0.529$ ), *Online Supplementary Table S2*.

There were no significant differences in the baseline characteristics of the four deprivation quartile groups in age at presentation, LDT and CD38 expression but less deprived patients presented with earlier stage (stage A/A0) disease ( $P=0.051$ ) - least deprived 90.9% *versus* most deprived 82.9%. There was also some albeit weak evidence for higher B2M levels in the more deprived quartile groups compared to the least deprived ( $P=0.067$ ), Table 1. Somewhat surprisingly, in

the least deprived quartile, there were fewer patients with adverse cytogenetics ( $P=0.054$ ). There was also some scant evidence that the two most deprived quartiles had a higher frequency of unmutated IGHV genes (31/89 - 34.8% vs. 35/132 - 26.5%,  $P=0.185$ ), Table 1.

Sixteen clinical therapeutic trials were open during 2005-2019 with 87 patients (38.2% of 228 patients requiring treatment) eligible and offered entry into a therapeutic clinical trial but

ten declined. There was no significant difference in the offering of clinical trials by clinicians or trial entry across the four WIMD quartiles ( $P=0.917$ ), *Online Supplementary Table S3*. This is the first study to assess not only the impact of deprivation on CLL outcomes but explore the possible underlying reasons. The major advantages of this single center study, is that all patients were managed in a free universal health care system, in specialist CLL clinics, according to national

**Table 1.** Prognostic marker frequency in the deprivation quartiles.

Prognostic markers	Most deprived N (%)	Second most deprived N (%)	Second least deprived N (%)	Least deprived N (%)	Total N (%)
<b>Age in years quartiles</b>	$\chi^2(9)=3.0802, P=0.961$				
<55	28 (22.8)	27 (19.7)	19 (20.0)	52 (16.9)	126 (19.0)
55-64	31 (25.2)	31 (22.6)	24 (25.3)	82 (26.7)	168 (25.4)
65-74	35 (28.5)	45 (32.8)	27 (28.4)	96 (31.3)	203 (30.7%)
≥75	29 (23.6)	34 (24.8)	25 (26.3)	77 (25.1)	165 (24.9)
Total	123 (100)	137 (100)	95 (100)	307 (100)	662 (100)
<b>Stage at diagnosis</b>	$\chi^2(6)=12.5161, P=0.051$				
Stage A/A0	102 (82.9)	114 (83.2)	83 (87.4)	278 (90.8)	577 (87.3)
Stage B	13 (10.6)	11 (8.0)	4 (4.2)	19 (6.2)	47 (7.1)
Stage C	8 (6.5)	12 (8.8)	8 (8.4)	9 (2.9)	37 (5.6)
Total	123 (100)	137 (100)	95 (100)	306 (100)	661 (100)
<b>CD38</b>	$\chi^2(3)=3.0638, P=0.382$				
CD38 <20%	69 (61.6)	86 (68.3)	51 (62.2)	188 (69.4)	394 (66.7)
CD38 ≥20%	43 (38.4)	40 (31.7)	31 (37.8)	83 (30.6)	197 (33.3)
Total	112 (100)	126 (100)	82 (100)	271 (100)	591 (100)
<b>LDT</b>	$\chi^2(3)=3.3796, P=0.337$				
<12 months	18 (17.8)	11 (9.8)	10 (12.3)	41 (15.4)	80 (14.3)
≥12 months	83 (82.2)	101 (90.2)	71 (87.7)	225 (84.6)	480 (85.7)
Total	101 (100)	112 (100)	81 (100)	266 (100)	560 (100)
<b>B2M</b>	$\chi^2(3)=7.1663, P=0.067$				
<3.5 mg/L	56 (61.5)	70 (69.3)	45 (67.2)	176 (75.9)	347 (70.7)
≥3.5 mg/L	35 (38.5)	31 (30.7)	22 (32.8)	56 (24.1)	144 (29.3)
Total	91 (100)	101 (100)	67 (100)	232 (100)	491 (100)
<b>Adverse cytogenetics</b>	$\chi^2(3)=7.6300, P=0.054$				
No	33 (80.5)	42 (66.7)	34 (85.0)	100 (82.6)	209 (78.9)
Yes	8 (19.5)	21 (33.3)	6 (15.0)	21 (17.4)	56 (21.1)
Total	41 (100)	63 (100)	40 (100)	121 (100)	265 (100)
<b>IGHV mutation status</b>	$\chi^2(3)=2.9748, P=0.396$				
<0.98	33 (70.2)	25 (59.5)	23 (74.2)	74 (73.3)	155 (70.1)
≥0.98	14 (29.8)	17 (40.5)	8 (25.8)	27 (26.7)	66 (29.9)
Total	47 (100)	42 (100)	31 (100)	101 (100)	221 (100)

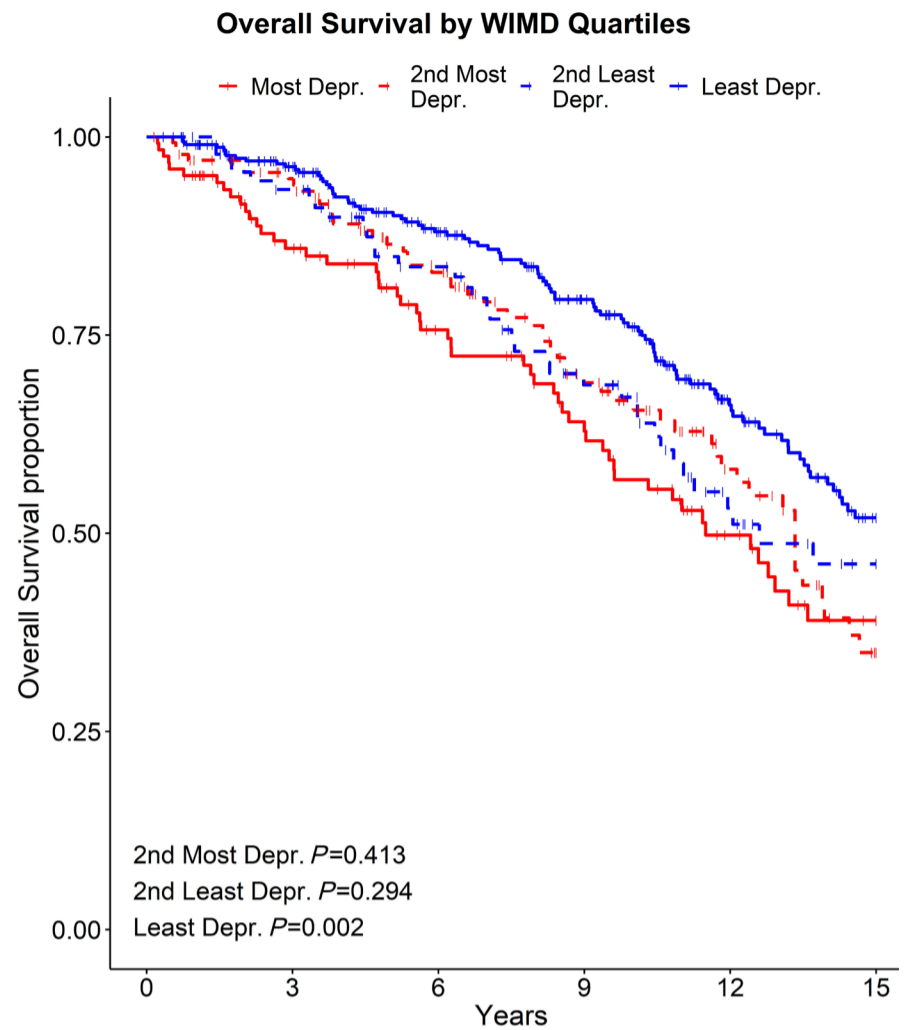
Adverse cytogenetics: deletion of 11q and/or 17p; Binet stage at diagnosis: stage A0 no lymphadenopathy, stage A lymphadenopathy <3 sites, stage B: 3 or more lymphoid site enlargements, stage C: hemoglobin <10 g/dL and/or platelets <100x10<sup>9</sup>/L; B2M: β-2 microglobulin; LDT: lymphocyte doubling time; IGHV: immunoglobulin heavy chain gene variable region.

guidelines with patients having access to global clinical trials, by a maximum of two specialists as type of care (primary, secondary or tertiary center) and access to specialists and clinical trials are known to impact CLL patient survival.<sup>4</sup> This study shows for the first time that deprivation leads to more advanced-stage disease at presentation and worse survival once therapy is initiated leading to a significantly worse overall survival and a possible link between deprivation and the well-established and very important CLL prognostic markers of high B2M and adverse cytogenetics (11q and 17p deletions).

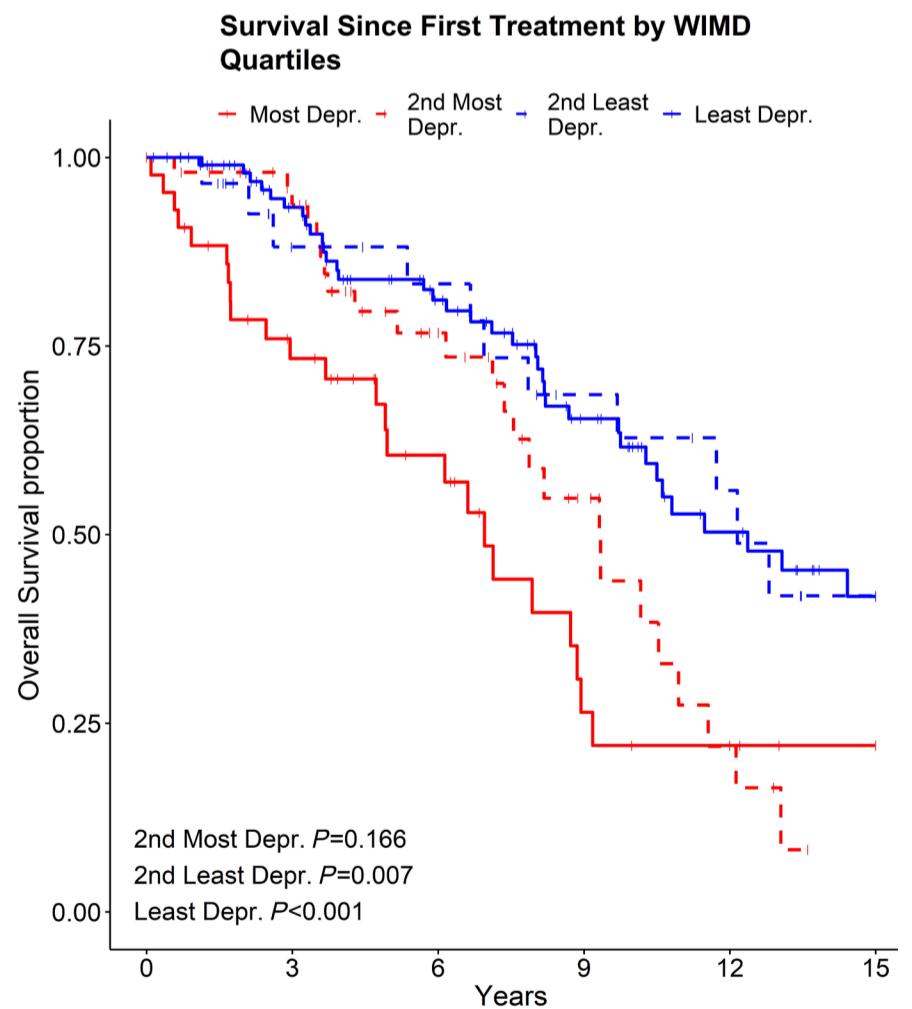
Why deprivation should impact the stage and age at presentation is unknown. Given the age at diagnosis for the most deprived is almost identical whether they presented with early- or advanced-stage disease (65 vs. 67 years) and that the least deprived group with advanced-stage disease presented 10 years younger (57 vs. 67 years) than the most deprived group, strongly suggests deprivation for whatever reason(s) leads to delayed presentation. Higher risk lifestyle behaviors e.g., smoking, obesity leading to other symptomatic illnesses increase with deprivation.<sup>5-9</sup> Comorbidities are very common in CLL patients and may mimic the vague symptoms of CLL and hence reassure the patient there is not another pathology, leading to a delay in presentation.<sup>10</sup> Alternatively, deprivation may increase fear of cancer or its treatments, alter the willingness of patients to take time off work to have their symptoms investigated, or perhaps may lead to inequalities in accessing health care, all of which would contribute to advanced-stage disease at presentation.<sup>5-9</sup>

Why deprivation should lead to worse overall clinical outcomes and worse outcomes once therapy has been initiated is also unknown. Comorbidities e.g., heart or lung disease etc. may contribute to a worse outcome once therapy is required by reducing the choices of available therapies or by reducing the duration or doses of therapy a patient may be able to tolerate. Furthermore, deprivation has been shown to impact patient compliance e.g., not attending hospital (routinely or urgently when unwell with infections) due to concerns about missing work and/or travel costs.<sup>5-9</sup> Deprivation is not routinely formally assessed in CLL patients requiring treatment but given the significant impact deprivation has on overall survival and survival from treatment, increased medical staff awareness, additional patient education and increased attention to any potential compliance issues an individual patient may have, may improve outcomes.

The higher B2M and the frequency of adverse cytogenetics may be due to more advanced-stage disease at presentation but the trend for deprivation to impact the frequency of unmutated IGHV genes (34.8% vs. 26.5%) perhaps suggests alternative possibilities that warrant larger studies to assess if deprivation alters the frequency of clinically impactful stereotypes (especially those associated with 11q and/or 17p deletions) or driver mutations.<sup>10-12</sup> For example, we know that as in other parts of the world, in Wales deprivation directly impacts air quality and that poor air



**Figure 1. Overall survival between four quartile deprivation groups.** WIMD: Welsh Index of Multiple Deprivation; Depr.: deprived.



**Figure 2. Survival since time of first treatment between four quartile deprivation groups.** WIMD: Welsh Index of Multiple Deprivation; Depr.: deprived.

quality can alter driver mutation expression.<sup>13,14</sup>

Finally, medical staff bias can also not be ruled out although this seems unlikely given that TTFT and access/participation into clinical trials is not significantly different between the deprivation groups.<sup>15</sup>

Great strides are being made in the treatment and outcomes of CLL patients with B-cell receptor and BCL-2 inhibitors, but if we wish to improve overall survival in all our CLL communities, then further research aimed at understanding and addressing the clinical impacts of social deprivation will be essential.

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### Disclosures

No conflicts of interest to disclose.

### Contributions

GF and DT analyzed data and wrote the manuscript. AD provided data. NE wrote the manuscript. CP analyzed samples, provided data and wrote the manuscript. CF conceived and devised study, contributed patient and clinical data, analyzed data and wrote the manuscript.

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### Data-sharing statement

The datasets generated during and/or analyzed during the current study are not publicly available as they contain personal patient information but are available from the corresponding author on reasonable request.