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

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

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**Disclosures**

All authors declare they have no conflicts of interest to disclose.

**Author Contributions**

GF - Analysed data and wrote manuscript.

DT - Analysed data and wrote manuscript.

AD - Provided data.

NE – Wrote manuscript.

CP – Analysed samples, provided data and wrote manuscript.

CF - Conceived and devised study, contributed patient and clinical data, analysed data and wrote manuscript.

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

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**Letter to the Editor**

Data from the Surveillance, Epidemiology, and End Results (SEER) database shows that CLL patients with higher social economic status have better outcomes but the reasons underlying this observation remain undetermined[1].

This single centre 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 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 5 parameter immunophenotyping scoring system[2]. Prognostic markers included clinical stage, lymphocyte doubling time (LDT), CD38 expression, B2M, IGHV mutation status at diagnosis with cytogenetic analysis (FISH) 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, Supplementary Table 1 [3].

The Welsh Government's Welsh Index of Multiple Deprivation (WIMD - last update 2019) provides a weighted (%) relative deprivation scoring system derived from 8 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 Square 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: 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, Supplementary Table 1.

There was significantly better overall survival with the least deprived having improved survival compared to the most deprived group (2nd most deprived HR 0.85 95% Confidence Interval (CI) [0.59, 1.25]; p=0.413, 2nd 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, analysing just those patients requiring treatment, survival from the time of first treatment, was significantly worse in the more deprived when comparing the 4 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 versus 67 years) ($p< 0.001$), Supplementary Table 2. Although there was no substantial difference in age at diagnosis for patients presenting with early-stage disease (65 versus 67 years - most versus least deprived $p=0.153$) across deprivation quartiles, the least deprived group with advanced stage disease presented 10 years younger (57 versus 67 years; $p=0.074$), Supplementary Table 2. Interestingly, the age at diagnosis for the most deprived is almost identical whether they presented with early or advanced stage disease (65 versus 67 years $p=0.835$) whereas there was a significant 10-year difference in the least deprived quartile (67 versus 57 years $p<0.001$), Supplementary Table 2. 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, Supplementary Table 2.

Analysing only the 263 patients who died, as expected advanced stage disease was associated with significantly earlier death (81 versus 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 ($p=0.529$), Supplementary Table 2.

There were no significant differences in the baseline characteristics of the 4 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% versus 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 10 declined. There was no significant difference in the offering of clinical trials by clinicians or trial entry across the 4 WIMD quartiles ($p=0.917$), Supplementary Table 3.

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 centre study, is that all patients were managed in a free universal health care system, in specialist CLL clinics, according to national guidelines with patients having access to global clinical trials, by a maximum of two specialists as type of care (primary, secondary or tertiary centre) and access to specialists and clinical trials are known to impact CLL patient survival[4]. 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 versus 67 years) and that the least deprived group with advanced stage disease presented 10 years younger (57 versus 67 years) than the most deprived group, strongly suggests deprivation for whatever reason(s) leads to delayed presentation. Higher risk lifestyle behaviours e.g. smoking, obesity leading to other symptomatic illnesses increase with deprivation[5-9]. 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[10]. Alternatively, deprivation may increase fear of cancer or it's 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[5-9].

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[5-9]. 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% versus 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[10-12]. For example, we know that as in other parts of the world, in Wales deprivation directly impacts air quality and that poor air quality can alter driver mutation expression[13,14].

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[15].

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.

## References


1. Nabhan C, Aschebrook-Kilfoy B, Chiu BC, et al. The impact of race, ethnicity, age and sex on clinical outcome in chronic lymphocytic leukemia: a comprehensive Surveillance, Epidemiology, and End Results analysis in the modern era. Leuk Lymphoma. 2014;55(12):2778-2784.

2. Moreau EJ, Matutes E, A'Hern RP, et al. Improvement of the chronic lymphocytic leukemia scoring system with the monoclonal antibody SN8 (CD79b). Am J Clin Pathol. 1997;108(4):378-382.

3. Schuh AH, Parry-Jones N, Appleby N, et al. Guideline for the treatment of chronic lymphocytic leukaemia: A British Society for Haematology Guideline. Br J Haematol. 2018;182(3):344-359.

4. Shanafelt TD, Kay NE, Rabe KG, et al. Hematologist/oncologist disease-specific expertise and survival: lessons from chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). Cancer. 2012;118(7):1827-1837.

5. McCutchan GM, Wood F, Edwards A, Richards R, Brain KE. Influences of cancer symptom knowledge, beliefs and barriers on cancer symptom presentation in relation to socioeconomic deprivation: A systematic review. BMC Cancer. 2015;15:1000.

6. Brown KF, Rumgay H, Dunlop C, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer. 2018;118(8): 1130-1141.

7. Quaife SL, Winstanley K, Robb KA, et al. Socioeconomic inequalities in attitudes towards cancer: An international cancer benchmarking partnership study. Eur J Cancer Prev. 2015;24(3):253-260.

8. Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: Evidence for common cancers. Br J Cancer. 2009;101 Suppl 2(Suppl 2):S92-S101.

9. Thurmes P, Call T, Slager S, et al. Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia. Leuk Lymphoma. 2008;49(1):49-56.

10. Stamatopoulos K, Belessi C, Moreno C. Over 20% of patients with chronic lymphocytic leukemia carry stereotyped receptors: Pathogenetic implications and clinical correlations. Blood. 2007;109(1):259-270.

11. Jaramillo S, Agathangelidis A, Schneider C, et al. Prognostic impact of prevalent chronic lymphocytic leukemia stereotyped subsets: analysis within prospective clinical trials of the German CLL Study Group (GCLLSG). Haematologica. 2020;105(11):2598-2607.

12. Landau DA, Wu CJ. Chronic lymphocytic leukemia: molecular heterogeneity revealed by high-throughput genomics. Genome Med. 2013;5(5):47.

13. Horton A, Jones SJ, Brunt H. Air pollution and public health vulnerabilities, susceptibilities and inequalities in Wales, UK. J Public Health (Oxf). 2023;45(2):432-441.

14. Hill W, Lim EL, Weeden CE, et al. Lung adenocarcinoma promotion by air pollutants. Nature. 2023;616(7955):159-167.

15. Sharrocks K, Spicer J, Camidge DR, Papa S. The impact of socioeconomic status on access to cancer clinical trials. Br J Cancer. 2014; 111(9):1684-1687.

**Table 1 Prognostic Marker Frequency in the deprivation quartiles**

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 – Haemoglobin <10g/dl and/or Platelets <100 x109/l.

B2M – Beta2Microglobulin

LDT – Lymphocyte Doubling Time - <12 - ≥12 months

IGVH - Immunoglobulin Heavy-chain gene Variable region

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

| Prognostic Markers n (%) | Most Deprived | 2nd Most Deprived | 2nd Least Deprived | Least Deprived | Total |
|---|---|---|---|---|---|
| **Age Quartiles** | **Chi2(9) = 3.0802, P-value = 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%) |
| **Stage at Diagnosis** | **Chi2(6) = 12.5161, P-value = 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%) |
| **CD38** | **Chi2(3) = 3.0638, P-value = 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%) |
| **LDT** | **Chi2(3) = 3.3796, P-value = 0.337** | | | | |
| <12 | 18 (17.8%) | 11 (9.8%) | 10 (12.3%) | 41 (15.4%) | 80 (14.3%) |
| ≥12 | 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%) |
| **B2M** | **Chi2(3) = 7.1663, P-value = 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%) |
| **Adverse Cytogenetics** | **Chi2(3) = 7.6300, P-value = 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%) |
| **IGVH Mutation Status** | **Chi2(3) = 2.9748, P-value = 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%) |

## Figure Legends

**Figure 1**

**Overall survival between 4 quartile deprivation groups.**

WIMD = Welsh Index of Multiple Deprivation

"Depr" = Deprived

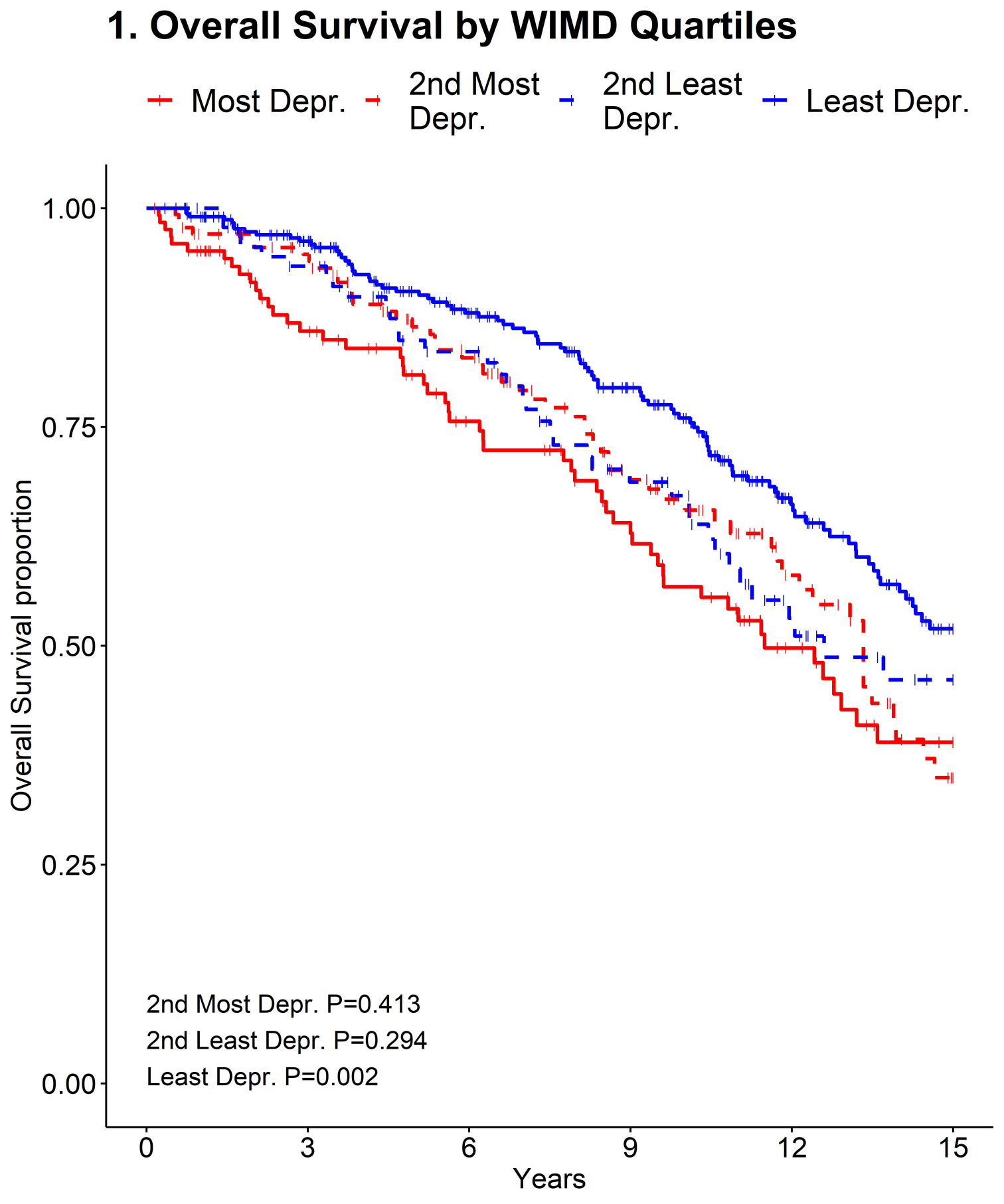
**Figure 2**

**Survival since Time of First Treatment between 4 quartile deprivation groups.**

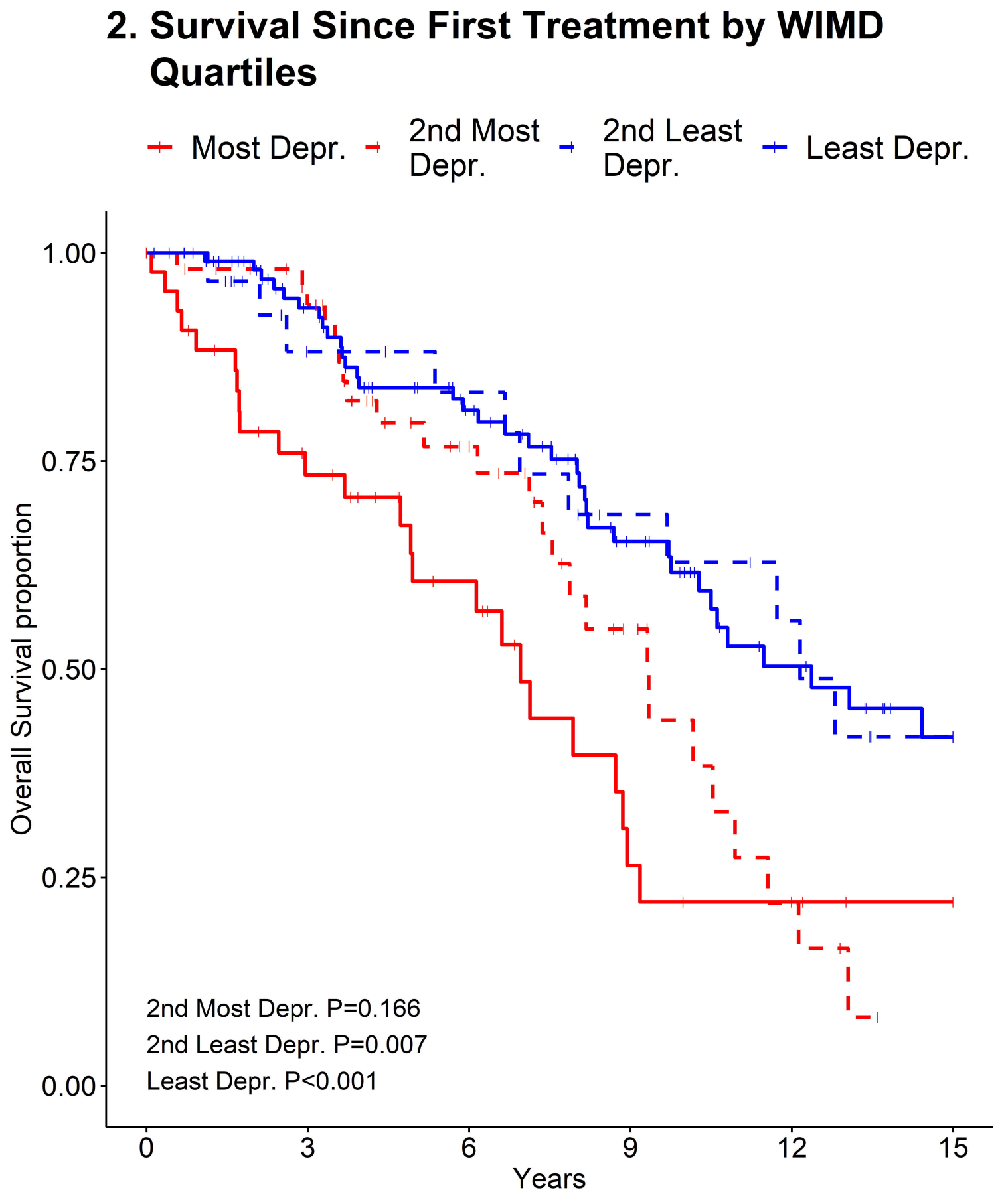
WIMD = Welsh Index of Multiple Deprivation

"Depr" = Deprived

# 1. Overall Survival by WIMD Quartiles



# 2. Survival Since First Treatment by WIMD Quartiles



**Supplementary Table 1 Hazard ratios for prognostic markers of overall survival**

| | Simple Model - 1 explanatory variable | Basic Multiple regression model | Basic model & LDT | Basic model & B2M | Basic model, B2M & Genetic | Basic model, B2M & Vh Status |
|---|---|---|---|---|---|---|
| **Welsh Index of Multiple Deprivation (N=662)** | **Reference = Most Deprived Hazard Ratio (HR), [95% C.I of HR], P-value** | | | | | |
| 2nd Most Deprived | 0.85 [0.59, 1.25] 0.413 | 0.80 [0.54, 1.18] 0.260 | 1.02 [0.63, 1.67] 0.924 | 1.07 [0.66, 1.75] 0.777 | 0.49 [0.23, 1.03] 0.058 | 0.81 [0.38, 1.73] 0.586 |
| 2nd Least Deprived | 0.80 [0.52, 1.22] 0.294 | 0.68 [0.43, 1.07] 0.097 | 0.96 [0.57, 1.62] 0.875 | 0.67 [0.37, 1.20] 0.177 | 0.42 [0.18, 0.96] 0.039 | 0.39 [0.15, 1.01] 0.052 |
| Least Deprived | 0.59 [0.42, 0.82] 0.002 | 0.57 [0.40, 0.81] 0.002 | 0.75 [0.48, 1.17] 0.203 | 0.71 [0.45, 1.12] 0.141 | 0.37 [0.19, 0.73] 0.004 | 0.5 [0.25, 1.00] 0.05 |
| **Age Quartiles (N=662)** | **Reference = <55 Years HR, [95% C.I of HR], P-value** | | | | | |
| 55-64 | 1.42 [0.88, 2.31] 0.155 | 1.59 [0.95, 2.66] 0.076 | 1.55 [0.80, 3.03] 0.197 | 1.34 [0.75, 2.41] 0.321 | 1.38 [0.73, 2.59] 0.316 | 1.70 [0.76, 3.79] 0.193 |
| 65-74 | 2.15 [1.38, 3.34] 0.001 | 2.20 [1.37, 3.53] 0.001 | 2.83 [1.56, 5.14] 0.001 | 1.80 [1.05, 3.09] 0.034 | 1.79 [0.95, 3.37] 0.073 | 2.15 [1.05, 4.39] 0.035 |
| ≥75 | 6.34 [4.11, 9.78] <0.001 | 7.99 [4.96, 12.87] <0.001 | 9.02 [5.00, 16.26] <0.001 | 8.05 [4.60, 14.07] <0.001 | 9.90 [4.30, 22.78] <0.001 | 8.17 [3.08, 21.65] <0.001 |
| **Stage at diagnosis (N=661)** | **Reference = A or A0 HR, [95% C.I of HR], P-value** | | | | | |
| B | 1.96 [1.28, 3.00] 0.002 | 2.79 [1.75, 4.44] <0.001 | 4.37 [2.22, 8.60] <0.001 | 2.51 [1.48, 4.25] 0.001 | 2.00 [1.07, 3.75] 0.030 | 2.04 [0.95, 4.38] 0.068 |
| C | 2.59 [1.70, 3.93] <0.001 | 4.38 [2.79, 6.86] <0.001 | 2.64 [0.80, 8.70] 0.112 | 2.85 [1.62, 5.01] <0.001 | 3.36 [1.71, 6.60] <0.001 | 3.75 [1.53, 9.23] 0.004 |
| **CD38 status (N=591)** | **Reference = <20 % HR, [95% C.I of HR], P-value** | | | | | |
| CD38 ≥20% | 1.90[1.45, 2.49]<0.001 | 1.84[1.39, 2.42]<0.001 | 1.43[1.03, 2.00]0.033 | 2.03[1.43, 2.88]<0.001 | 1.86[1.11, 3.13]0.019 | 2.21[1.25, 3.91]0.006 |
| **LDT (N=560)** | **Reference >= 12 HR, [95% C.I of HR], P-value** | | | | | |
| <12 | 2.08 [1.43, 3.01] <0.001 | | 1.43 [0.94, 2.18] 0.090 | | | |
| **B2M (N=491)** | **Reference = < 3.5 HR, [95% C.I of HR], P-value** | | | | | |
| ≥3.5 mg/l | 2.48 [1.81, 3.40] <0.001 | | | 2.05 [1.44, 2.94] <0.001 | 1.48 [0.90, 2.45] 0.126 | 1.55 [0.91, 2.64] 0.110 |
| **Adverse Cytogenetics (N=265)** | **Reference NOT (ATM and/or P53 deletions) HR, [95% C.I of HR], P-value** | | | | | |
| ATM and/or P53 deletion | 2.51 [1.62, 3.89] <0.001 | | | | 1.81 [1.04, 3.18] 0.037 | |

| IGVH Status (N=221) | Reference = <0.98 Hazard Ratio, [95% C.I of HR], P-value) | | | | | |
|---|---|---|---|---|---|---|
| ≥0.98 | 2.24 [1.48, 3.41] <0.001 | | | | | 2.14 [1.19, 3.84] 0.011 |
| Observations | | 590 | 505 | 439 | 224 | 160 |

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 – Haemoglobin <10g/dl and/or Platelets <100 x109/l.

B2M – Beta2Microglobulin

LDT – Lymphocyte Doubling Time - <12 - ≥12 months

IGVH - Immunoglobulin Heavy-chain gene Variable region

**Supplementary Table 2 Age at Diagnosis and Death**

| WIMD Quartiles | Age at Diagnosis | | | | | | | Age at Death | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall Cohort | | Subgroup: Stage A/A0 diagnosis | | Subgroup: Stage B/C diagnosis | | Mann-Whitney U Test (Stages A/A0 & B/C) | Overall Cohort | | Subgroup: Stage A/A0 diagnosis | | Subgroup: Stage B/C diagnosis | | Mann-Whitney U Test (Stages A/A0 vs B/C) |
| | Median age [p25, p75] | n | Median age [p25, p75] | n | Median age [p25, p75] | n | | Median age [p25, p75] | n | Median age [p25, p75] | n | Median age [p25, p75] | n | |
| Most Deprived | 65 [56, 74] | 123 | 65 [57, 73] | 102 | 67 [52, 77] | 21 | 0.835 | 79 [67, 86] | 58 | 79.5 [69, 86] | 40 | 77.5 [61, 81] | 18 | 0.102 |
| 2nd Most Deprived | 67 [57, 74] | 137 | 68 [57, 76] | 114 | 59 [51, 73] | 23 | 0.041 | 80 [67, 86] | 61 | 80 [67, 87] | 47 | 70.5 [62, 81] | 14 | 0.073 |
| 2nd Least Deprived | 65 [58, 75] | 95 | 68 [58, 76] | 83 | 61 [57.5, 64] | 12 | 0.114 | 81.5 [69, 87] | 42 | 82 [72, 88] | 35 | 65 [63, 75] | 7 | 0.003 |
| Least Deprived | 67 [57, 75] | 307 | 67 [58, 75] | 278 | 57 [52.5, 65] | 28 | <0.001 | 80 [74, 87] | 102 | 81 [77, 88] | 87 | 72 [65, 75] | 14 | <0.001 |
| Overall Cohort | 67 [57,74] | 662 | 67 [58, 75] | 577 | 60 [52, 69.5] | 84 | <0.001 | 80 [70, 86] | 263 | 81 [74, 87] | 209 | 71 [62, 79] | 53 | <0.001 |
| Mann-Whitney U Test (Most vs Least Deprived) | 0.420 | | 0.153 | | 0.074 | | | 0.052 | | 0.077 | | 0.529 | | |

WIMD = Welsh Index of Multiple Deprivation

**Supplementary Table 3 Clinical therapeutic studies offered to patients**

| Clinical Trial n (%) | Most Deprived | 2nd Most Deprived | 2nd Least Deprived | Least Deprived | Total |
|---|---|---|---|---|---|
| No (not offered/entered a trial) | 28 (22.76) | 31 (22.63) | 15 (15.79) | 67 (21.82) | 141 (21.3) |
| Yes (entered a trial) | 13 (10.57) | 18 (13.14) | 12 (12.63) | 34 (11.07) | 77 (11.63) |
| Eligible but did not enter a trial as declined offer of a trial | 2 (1.63) | 3 (2.19) | 2 (2.11) | 3 (0.98) | 10 (1.51) |
| Not Applicable | 80 (65.04) | 85 (62.04) | 66 (69.47) | 203 (66.12) | 434 (65.56) |
| Total | 123 (100) | 137 (100) | 95 (100) | 307 (100) | 662 (100) |

Chi2(9) = 3.9117, P-value = 0.917