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Prior lymphopenia is associated with mortality in primary care pneumonia: a cohort study.

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Key words:
Primary care, lymphopenia, biomarker, infection, respiratory, pneumonia.
Abstract:

Background

Lymphopenia (reduced lymphocyte count) during infections such as pneumonia is common and is associated with increased mortality. Little is known about the relationship between lymphocyte count prior to developing infections and mortality risk.

Aim:

To identify whether patients with lymphopenia who develop pneumonia have increased risk of death.

Design and Setting:

A cohort study in the Clinical Practice Research Datalink (CPRD), linked to national death records. This database is representative of the UK population, and is extracted from routine records.

Methods:

Patients aged >50 years with a pneumonia diagnosis were included. We measured the relationship between lymphocyte count and mortality, using a time-to-event (multivariable Cox regression) approach, adjusted for age, sex, social factors, and potential causes of lymphopenia. Our primary analysis used the most recent test prior to pneumonia. The primary outcome was 28 day, all-cause mortality.

Results:

40,909 participants with pneumonia were included from 1998 until 2019, with 28,556 having had a lymphocyte test prior to pneumonia (median time between test and diagnosis 677 days). When lymphocyte count was categorised (0-1×10^9/L, 1-2×10^9/L, 2-3×10^9/L, >3×10^9/L, never tested), both 28-day and one-year mortality varied significantly: 14%, 9.2%, 6.5%, 6.1% and 25% respectively for 28-day mortality, and 41%, 29%, 22%, 20% and 52% for one-year
mortality. In multivariable Cox regression, lower lymphocyte count was consistently associated with increased hazard of death.

Conclusion

Lymphopenia is an independent predictor of mortality in primary care pneumonia. Even low-normal lymphopenia (1-2×10⁹/L) is associated with an increase in short- and long-term mortality compared with higher counts.

How this fits in:

Low lymphocyte levels during infection are common and associated with increased risk of death. This study, in a representative British primary care population, shows that having a low lymphocyte count before getting infection - even years before - is also associated with an increased risk of dying.
Introduction:

Lymphopenia (a reduction in the normal concentration of lymphocytes), has long been implicated as a potential biomarker in acute infection; many studies show that lymphopenia during or at the start of infection is associated with poor outcomes.\(^1\)\(^-\)\(^4\) Exploring the mechanisms and therapeutic implications of this phenomenon has been the subject of recent reviews, and remains largely unexplained.\(^5\)\(^,\)\(^6\)

Recent work has also shown that lymphopenia may predict infection, and infection-related mortality, even when the test significantly precedes the infection, with some studies supporting an increased risk of a wide range of infections (including pneumonia) and infection-related mortality, although no work has been performed in the broader primary care population with pneumonia.\(^7\)\(^,\)\(^8\)

Respiratory infections such as pneumonia are very common in primary care\(^9\), and greater understanding of predictive features would be of significant value to clinicians.

In this study, we estimated the effect of lymphocyte counts on mortality in a large, unselected, primary care population with primary-care coded pneumonia.

Methods:

This study was performed in the Clinical Practice Research Datalink (CPRD), a large, representative UK primary care database, which holds coded primary care electronic health records, including blood tests, prescriptions, diagnostic codes, and immunisations. 70% of English practices in this database are linked to the Office for National Statistics (ONS) mortality data, a national death registry. Ethical approval was given by the CPRD Independent Scientific Advisory Committee (ISAC ref. 18_276R).

Analysis was conducted and reported in line with the STROBE guidance (appendix 2)

Participants

Participants in this study were included from January 1998 until January 2019, had a coded diagnosis of pneumonia, and were over 50 years of age at the time of diagnosis of pneumonia. No other clinical exclusion criteria were used. CPRD records were included if they were considered of ‘up to standard’ and ‘acceptable’ quality (both internal CPRD metrics) for 6 months prior to pneumonia diagnosis.

If participants had multiple pneumonia episodes, the first was taken.
Outcomes

The primary outcome in this study was 28-day mortality, with a secondary outcome of one-year mortality following pneumonia diagnosis.

Lymphopenia definition

Blood test data is automatically extracted from GP medical records into the CPRD, with tests performed on a variety of platforms, across multiple laboratories in England. All laboratory results are used for routine clinical work, and there is likely to be limited relevant laboratory variation for this assay. The result and date of the test were extracted, and extreme values (>10×10^9/L) were removed as outliers.

As most patients had multiple lymphocyte tests, we considered several strategies to define lymphocyte count for the subsequent analysis. Our primary analysis was simply the most recent count, with no restrictions on time from blood test until pneumonia. We arbitrarily categorised this into integer cut points (<1×10^9/L, 1 - 2×10^9/L, 2-3×10^9/L, and >3×10^9/L) for ease of clinical interpretation for our primary analysis.

Multiple other approaches for quantifying lymphocyte count were performed, with details in the sensitivity analysis below.

Confounding variables

As lymphocyte counts and mortality from pneumonia are known to be related to many common patient-level factors, relevant confounders were extracted from the CPRD. These included specific medical comorbidities, smoking status, alcohol usage, corticosteroid use, age (at time of pneumonia diagnosis), and area-based socioeconomic deprivation (index of multiple deprivation, IMD).

Medical comorbidities were included that are known to impact on lymphocyte count or mortality from pneumonia: cancer, autoimmune disease, organ transplantation, stem cell transplantation, HIV disease, previous stroke, diabetes (any type), peripheral vascular disease and previous myocardial infarction.

For all comorbidities except cancer, these were defined based on any relevant diagnostic code recorded prior to the pneumonia (not the lymphocyte test, as the condition may not yet be diagnosed at the time of testing). For cancer, any (excluding non-melanotic skin cancer) code in the preceding 2 years was taken as evidence of cancer.

Smoking status was categorised into never smoker, current smoker, or ex-smoker based on clinical codes, and alcohol use defined by the presence of a variety of diagnostic codes for
increased alcohol consumption. In patients without any smoking related codes, smoking status was coded as “unknown”.

Corticosteroid use was defined as the prescription of more than two issues of an oral corticosteroid over the last 12 months, irrespective of dose or duration of issue. Finally, we included calendar year as a continuous variable, as management of pneumonia and testing may have changed over the period of the study.

**Statistical approach**

Initially, patients who had ever had lymphocyte tests were compared with those who had never been tested, to identify any biases related to testing within the dataset.

Subsequently, our primary analysis was a Cox regression to calculate hazard ratios, adjusted for the aforementioned covariates. Both non-adjusted and adjusted Kaplan-Meir curves were generated, with the adjusted plots generated with the marginal approach, allowing for differential weighting of subgroups.\(^{10}\)

Lymphocyte count was treated as a categorical variable (cut at integer breakpoints for ease of clinical interpretation). Only patients with a recorded result were included in the primary analysis. Age was modelled as a linear variable. Smoking status and IMD were modelled as categorical variables. All other covariates were treated as binary. Very rare variables (<50 occurrences) were removed. As a secondary analysis, and for the purposes of visualisation, a restricted cubic spline Cox model was generated using lymphocyte count as a continuous variable.

As ‘up to standard’ CPRD data is relatively complete, and we defined diagnosis by the presence of a code, missing data was relatively rare. As such, we performed a complete case analysis. We censored follow-up at 1 year. All analysis was performed in R 3.6.1, using the packages “tidyverse”, “survival”, “broom”, “Hmisc” and “survminer”, with table generation using “tidyverse” and “gtsummary”.\(^{10–12}\)

**Sensitivity analyses**

As many patients had multiple tests, we explored multiple alternative approaches to defining lymphocyte count, categorising lymphocyte count based on quartiles rather than integer cut-points, and additionally using alternative choice of measurements (i.e. excluding measurements over 1-year prior to pneumonia diagnosis; excluding measurements less than 6-months prior to pneumonia diagnosis; using the first ever measurement; and selecting the maximum, minimum and mean counts irrespective of time).

In order to consider the potential bias generated by testing, we generated a subsequent Cox model including patients who had never had a lymphocyte count prior to pneumonia.
Finally, we included length of time between the most recent test and pneumonia as an interaction term with lymphocyte count.

Results

**Participant demographics**

40,909 participants were included in this study. Demographics are listed in Table 1, comparing patients who had ever had a lymphocyte count (n = 35,690) with participants never tested (n = 5,219).

Participants who had no blood tests recorded were generally slightly older than other participants, but with lower rates of all comorbidities. Remarkably, patients who had never had a lymphocyte test had a significant one-year mortality of 52%, suggesting the tested group are significantly different to non-tested.

**Lymphocyte testing timings and distributions**

Across the 35,690 patients tested, 366,870 tests were performed. Patients had a median of 7 (IQR 3–13) tests and the distribution of tests was highly skewed to the left. The maximum number of tests on one person was 287, although the vast majority of patients had far fewer.

Testing steadily increased prior to diagnosis, with the peak number of tests just prior to pneumonia diagnosis (Supplementary Figure 1, appendix). This was also highly skewed, with a median time from test of 525 days (IQR 10–1,720). Lymphocyte test results were essentially normally distributed, with a mean (SD) of 1.85 (0.88) × 10^9/L, as demonstrated in Figure 1.

There was no clear relationship between numbers of tests and lymphocyte count (Supplementary Figure 2, appendix).

**Relationship between lymphocyte count and mortality**

For our main analysis, the most recent lymphocyte count prior to pneumonia was chosen. This limited the sample size to 28,556 patients, as 7,124 participants only had lymphocyte counts measured after or on the date of pneumonia diagnosis and were excluded. Of those 28,556 patients, 2,601 (7.3%) patients met the primary outcome (died within 28 days), and 8,377 (23%) met the secondary outcome (died within a year).
There was a clear relationship between lymphocyte count and both outcomes. Figure 3 shows the relationship with increased mortality from the restricted cubic spline model, showing a non-linear increase in risk with decreasing lymphocyte count.

Crude mortality figures for each integer cut off are presented in Table 2, which show a clear decrease in risk with increasing lymphocyte count.

**Cox regression**

Multivariable Cox regression was undertaken, with mortality censored at either 28-days (primary outcome) or one-year (secondary outcome) (Table 3). Due to low numbers of cases, HIV status and Stem Cell Transplantation were removed from the Cox model.

There was a clear association between having low lymphocyte count and increased risk of death at 28-days post-pneumonia, with an adjusted hazard ratio (95%CI) of 1.63 (1.44 -1.84) for lymphocyte counts <1×10^9/L compared to 2-3×10^9/L. A similar effect was observed for 1-year mortality (adjusted HR 1.59,1.48 -1.71). Unsurprisingly, most comorbidities were also associated with increased mortality, except autoimmunity and ischaemic heart disease, which were both associated with reduced mortality at both 28-days and one-year. Corresponding Kaplan-Meir survival curves are shown in Figure 3 (adjusted) and appendix Supplementary Figure 3 (unadjusted).

**Sensitivity analyses**

For the quartile model, full Cox regression outputs for the primary outcome are shown in Table S1, in the appendix. Briefly, there remained a strong relationship with mortality, with the hazard ratio for death for those in the lowest quartile [0.09 - 1.31 x 10^9/L] of 1.56 (1.39-1.74). 28-day mortality was 13% and 6.1% in the lowest and highest quartiles of lymphocyte count respectively (Supplementary Table 2, appendix).

Abbreviated results (hazard ratio for lymphocyte count only) of models using alternative exposure definitions are presented in Supplementary Table 3, appendix. These associations were also maintained when the timing of testing was varied; the strongest association between lymphopenia and mortality was observed when only measurements in the past year were included (HR, 95%CI) 1.57 (1.45-1.69) for lowest vs highest quartile of lymphocyte count), and the weakest association was observed when either the first measurement or mean measurement was used ( 1.29 (1.21-1.37)). The association was maintained (1.37 (1.28-1.47)) when measurements in the 6-months prior to pneumonia were excluded to ensure results were not directly related to the pneumonia itself.

Finally, the association persisted when the minimum, maximum or mean lymphocyte count was used; the minimum count showed a stronger association(HR, 95% CI 1.58 (1.44-1.68)). Unsurprisingly, the time between lymphocyte test and pneumonia varied significantly with each
In the “first ever” approach, the median time from test until pneumonia was 1,720 days.

In summary, the association between alternative definitions of lymphocyte count and outcomes was maintained, however, the association was strongest when using lymphocyte tests that were closely temporally related to the pneumonia diagnosis, and when taking the minimum ever recorded lymphocyte count.

In the sensitivity analysis including patients who had never had a lymphocyte test (n = 5,219) in the model, risk estimates were similar, with a HR (95%CI) of 1.66 (1.47-1.88) for a lymphocyte count of 0-1 x10^9/L, compared to the reference (2-3 x 10^9/L).

There was no evidence from the interaction model that the strength of association between lymphocyte count and mortality was modified by time-to-test or number of tests.

Discussion:

Summary

In this large primary care cohort of patients with pneumonia, there is a clear relationship between low lymphocyte count and increased mortality. In particular, even mild lymphopenia, within the defined normal range, (lymphocyte count between 1 and 2×10^9/L) is associated with a significant increase in both short- and longer-term mortality.

Strengths and limitations

This study has many strengths. Firstly, the large-scale cohort used a nationally representative UK primary care dataset, linked to mortality data. Secondly, the large number of patients (~29,000) allow for firm conclusions about risk estimates, and the quality of CPRD coding enables testing for multiple covariates, none of which substantially altered the hazard estimate. Thirdly, the wide variety of approaches to defining lymphocyte count provide reassurance that this is not simply a testing phenomenon. In particular, even definitions using relatively historic (e.g. first ever lymphocyte count) results showed an association with subsequent pneumonia mortality. This study has weaknesses consistent with similar observational analyses of large routine datasets. In particular, we do not have information on why tests were performed, although we did not find an interaction between number of tests and the outcome. It is also important to note that around 15% of patients did not have a recorded test, and this population was quite different to the tested population, with a 52% one year mortality. Secondly, although we included a broad range of confounding variables, it is possible that other causes for lymphopenia are not recorded (e.g. moderate alcohol intake not reported to GP). Despite this,
unadjusted and adjusted risk estimates were broadly similar. Thirdly, our cohort comprised patients over 50 years old at the time of pneumonia diagnosis, and it is therefore necessary to be cautious about extrapolating to younger individuals.

Comparisons with existing literature

There has been significant research interest in lymphopenia as a marker of poor immune function, although much work is pre-clinical, focusing on potential mechanisms of immune dysfunction.\(^5\) It remains unclear whether lymphopenia represents chronic failure of the immune system, or simply dysregulation. Some studies have found significant apoptosis of lymphocytes after infection, and this perhaps reflects dysregulation of immune control, rather than failure to maintain lymphocyte counts.\(^5,14\) It is also well established that lymphopenia occurs in critical illness, and it may be that lymphopenia simply represents an epiphenomena of sickness, although we did adjust for other markers of sickness in our study\(^7\).

In clinical data, one Oxford-based cohort study of adult emergency admissions, lymphopenia was shown to be an independent predictor of bacteraemia, although with modest performance (Area under the curve 0.63).\(^1\) In a large, Danish, population study of 98,344 invited individuals in Copenhagen, lymphopenia (defined as \(<1.1\times10^9/\text{L}\) was associated with a significant increase in infection and infection-related death (adjusted hazard ratios of 1.41 (95% CI 1.28–1.56) for any infection, 1.70 (95% CI 1.37–2.10) for infection-related death.\(^8\) Of note, only 2,352 (~3%) of individuals had lymphopenia at this examination by their definition, and this was an invited population study, hence mortality was much reduced from our study (5,636 deaths (5.7%) at median follow up of 6 years). Of note, in contrast to our own study, increased mortality was not associated with low-normal lymphopenia (1-2×10^9/L). Another, recent, US study on a large invited cohort (the National Health and Nutrition Examination Survey) of 31,178 individuals found a relationship between lymphopenia and mortality, with a multivariable adjusted hazard ratio of 1.8 (95% CI 1.6 - 2.1) for all-cause mortality with severe lymphopenia (lymphocyte count \(<1\times10^9/L\)).\(^15\) Of note, this also relied on a single measure, and only half of patients included had linked mortality data, raising concern for bias.

Other work has focused on lymphopenia after diagnosis in infection as a poor prognostic marker,\(^2,3,16\) with one study in pneumonia (n = 3,043) finding lymphopenia as a predictor of early, but not late mortality, in contrast to our findings\(^3\). In another study\(^16\), severe lymphopenia (<0.744 x 109/L) was tested as an addition to CURB-65, a prognostic tool for pneumonia\(^17\), modestly improving the predictive performance (C-statistic increased from 0.722 - 0.739) in a validation cohort.

In both studies in secondary care lymphopenia may represent acute illness, in contrast to our setting, where lymphopenia is more likely to be chronic.\(^4\)

As far as we are aware, no studies have been performed in primary care looking at lymphopenia with a focus on pneumonia, which has significant implications. Firstly, the vast majority of
patients with respiratory tract infection present to primary care, and risk stratification here is critical. Secondly, the potential for identification and potential therapeutics is greater than in the secondary care, as discussed below.

Implications for research and/or practice

This study suggests lymphopenia is associated with both short and long term mortality. This has implications for risk stratification and for future therapeutics. For risk stratification, this study suggests that even low-normal lymphopenia should be considered as a part of triage in identifying those likely to die. Further studies should evaluate this with other markers and scores for predicting outcome in pneumonia, such as CURB-65. Alongside this, the role of lymphopenia in predicting occurrence and outcome of infection should be studied. Finally, the dramatic one-year mortality (52%) in the non-tested group provides further evidence that indications for testing can strongly alter the predictive value of testing, and clinicians should take this into account when interpreting this study.

For therapeutics, researchers should focus on identifying whether this is an epiphenomenon, or represents an opportunity to intervene in a dysregulated immune system. In particular, more accurate characterisation of lymphocyte functionality in pneumonia would be of significant value in assessing whether this is a therapeutic target.

Conclusions:

Lymphopenia is robustly associated with short and long term survival in pneumonia, with increasing risk with lower lymphocyte counts. Patients with low-normal lymphocyte counts (1-2 x 10^6/ml) are at significantly increased risk of mortality.

Data sharing:

The MHRA do not allow sharing of raw CPRD data. If access is required, ISAC can be contacted to generate similar datasets.

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Table 1: Demographics of participants included in the study.

| Characteristic                        | Never tested, N = 5,219 | Tested, N = 39108 | p-value 2 |
|---------------------------------------|--------------------------|-------------------|-----------|
| Age                                   | 81 (69, 88)              | 76 (66, 85)       | <0.001    |
| Female Gender                         | 2740 (53%)               | 18020 (50%)       | 0.007     |
| Diabetes                              | 421 (8.1%)               | 5404 (15%)        | <0.001    |
| HIV status                            | 2 (<0.1%)                | 22 (<0.1%)        | 0.8       |
| Ischaemic Heart Disease               | 829 (16%)                | 7093 (20%)        | <0.001    |
| Ischaemic Stroke                      | 1030 (20%)               | 5337 (15%)        | <0.001    |
| Alcohol excess                        | 98 (1.9%)                | 834 (2.3%)        | 0.043     |
| Autoimmunity                          | 505 (9.7%)               | 6054 (17%)        | <0.001    |
| Corticosteroid user                   | 467 (8.9%)               | 5134 (14%)        | <0.001    |
| Peripheral vascular disease           | 227 (4.3%)               | 1844 (5.2%)       | 0.013     |
| Stem Cell Transplant                  | 3 (<0.1%)                | 17 (<0.1%)        | 0.7       |
| Solid Organ Transplant                | 9 (0.2%)                 | 130 (0.4%)        | 0.036     |
| Cancer (solid organ)                  | 224 (4.3%)               | 1692 (4.7%)       | 0.2       |
| Haematological cancer                 | 36 (0.7%)                | 393 (1.1%)        | 0.008     |
| Smoking Status                        |                          |                   | <0.001    |
| Never smoker                          | 1594 (31%)               | 8021 (22%)        |           |
| Ex smoker                             | 920 (18%)                | 16165 (45%)       |           |
| Current smoker                        | 467 (8.9%)               | 3368 (9.4%)       |           |
| Unknown                               | 2238 (43%)               | 8136 (23%)        |           |
### Table 2: Crude mortality for each integer cut off for lymphocyte count.

| Lymphocyte count (×10⁹/L) | 0-1, N = 3,931 | 1-2, N = 14,963 | 2-3, N = 7,419 | >3, N = 2,243 |
|---------------------------|----------------|----------------|----------------|--------------|
| Primary outcome: 28-day mortality | n (%) | n (%) | n (%) | n (%) |
| 0-1                       | 548 (14%) | 1375 (9.2%) | 485 (6.5%) | 136 (6.0%) |
| 1-2                       | 1,156 (29%) | 4,276 (28%) | 1,627 (22%) | 456 (20%) |

### Table 3: Adjusted Cox Regression outputs for 28-day and 1 year mortality.

| Characteristic | 28-day mortality | | 1-year mortality | |
|----------------|------------------|------------------|------------------|------------------|
|                | HR² | 95% CI | p-value | HR² | 95% CI | p-value |
| Lymphocyte count (×10⁹/L) | | | | | |
| 0-1             | 1.63 | 1.44, 1.84 | <0.001 | 1.59 | 1.48, 1.71 | <0.001 |
| 1-2             | 1.15 | 1.03, 1.27 | 0.009 | 1.14 | 1.08, 1.21 | <0.001 |

1 Statistics presented: median (IQR); n (%)
2 Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independence; Fisher’s exact test
| Condition                        | Hazard Ratio | 95% CI       | p-Value | Hazard Ratio | 95% CI       | p-Value | Hazard Ratio | 95% CI       | p-Value |
|---------------------------------|--------------|--------------|---------|--------------|--------------|---------|--------------|--------------|---------|
| >3                              | 0.95         | 0.78, 1.15   | 0.6     | 0.91         | 0.82, 1.01   | 0.069   |              |              |         |
| Female Gender                   | 10.99        | 0.92, 1.090.91, 1.07 | <0.001 | 0.86         | 0.82, 0.90   | <0.001  |              |              |         |
| Age                             | 1.061        | 1.06, 1.071.06, 1.06 | <0.001< 0.001 | 1.06         | 1.05, 1.06   | <0.001  |              |              |         |
| Diabetes                        | 0.990        | 0.89, 1.110.85, 1.07 | 0.90 | 1.07         | 1.00, 1.13   | 0.034   |              |              |         |
| Ischaemic Heart Disease         | 0.820        | 0.74, 0.910.76, 0.92 | <0.001< 0.001 | 0.98         | 0.93, 1.03   | 0.5     |              |              |         |
| Ischaemic Stroke                | 1.411        | 1.28, 1.531.29, 1.55 | <0.001< 0.001 | 1.29         | 1.22, 1.36   | <0.001  |              |              |         |
| Peripheral vascular disease     | 0.960        | 0.81, 1.140.82, 1.15 | 0.60 | 1.09         | 1.00, 1.18   | 0.064   |              |              |         |
| Alcohol excess                  | 1.531        | 1.15, 2.031.09, 1.92 | 0.0030 10 | 1.32         | 1.13, 1.55   | <0.001  |              |              |         |
| Autoimmunity                    | 0.870        | 0.78, 0.970.77, 0.95 | 0.0110 05 | 0.92         | 0.87, 0.98   | 0.007   |              |              |         |
| Solid Organ Transplant          | 0.960        | 0.40, 2.310.37, 2.16 | >0.90 | 1.13         | 0.75, 1.69   | 0.6     |              |              |         |
| Cancer (solid organ)            | 2.832        | 2.50, 3.212.44, 3.13 | <0.001< 0.001 | 2.95         | 2.75, 3.17   | <0.001  |              |              |         |
| Haematological cancer           | 0.960        | 0.65, 1.430.64, 1.42 | 0.80 | 1.75         | 1.47, 2.08   | <0.001  |              |              |         |
| Smoking status          | Hazard Ratio (HR) | Confidence Interval (CI) | p-value |
|-------------------------|-------------------|--------------------------|---------|
| Never smoker (reference) | —                 | —                        | 0.12    |
| Ex smoker               | 0.970            | 0.86, 1.080.76, 0.95     | 0.5003  |
|                        | 1.460.9          | 1.34, 1.600.92, 1.04     | <0.001  |
| Current smoker          | 1.41.36          | 1.19, 1.4151.61, 1.61    | <0.001  |
|                        | 1.51.4           | 1.17, 1.341.31, 1.57     | <0.001  |
| Unknown                 | 1.431            | 1.28, 1.601.25, 1.57     | <0.001  |
|                        | 1.051.2          | 0.99, 1.121.16, 1.32     | 0.12<0.001 |
| Calendar year           | 0.95             | 0.94, 0.96               | <0.001  |
|                        | 0.97             | 0.96, 0.97               | <0.001  |

1 HIV status and Stem Cell Transplant removed as few instances, Index of Multiple Deprivation not shown for brevity. 2 HR = Hazard Ratio, CI = Confidence Interval.
Figure 1: Distribution of lymphocyte counts across all tests (396,872 tests) across the whole population.
Figure 2: Restricted cubic spline model showing relationship between Lymphocyte count and survival at 28-days (A) and 1 year (B).
Figure 3: 1-year Survival from pneumonia, stratified by lymphocyte count and adjusted for confounders
Publishing a research paper is only the first part of the process of helping patients. It is important to disseminate your research so that it can be implemented in practice and make an impact. And, of course, the "impact" of your research is a key component in any research assessment. We can help you do this, please supply the following:

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| Corresponding author | Please add the corresponding author name | Hamilton |
| Author details | Please consult each co-author and CONFIRM (by stating 'I/we confirm') that the following details on the Manuscript/title page and the submission system are correct: (1) order of authors (2) spelling of names, (3) qualifications, (4) job titles, and (5) affiliations. Your confirmation must apply to all authors. | Can we change Rupert Payne from FRCP to FRCPE? Rest is fine - we CONFIRM. |

**Essential fields *  
Questions for authors to help promote your research:**

| Essential fields * | Word count | Questions for authors to help promote your research |
|--------------------|------------|----------------------------------------------------|
| Print article summary* | min 10, max 25 words | How would you describe your research in one sentence? Please avoid saying: “we undertook a randomised controlled trial…”, more like “Primary care patients treated with oseltamivir recovered from influenza-like illness one day sooner than usual care.” Patients with lymphopenia had significantly increased short and long term mortality in pneumonia. |
| How this fits in* (research statement) | min 50, max 100 words | How does your study fit into what is currently known in this field of research? Summarise, in no more than four short sentences, what was previously known or believed on the topic and what your research adds, particularly focusing on relevance to clinicians. Pneumonia is associated with a significant mortality burden. Lymphopenia has previously been associated with immune dysfunction. This study shows that even "low-normal" lymphocyte counts are associated with increased mortality. Risk increases with lower lymphocyte counts. |
| Clinical impact* (clinical statement) | min 3, max 15 words | What is the impact of your research in a clinical settings? If your findings were implemented, what would be the clinical impact? e.g. ‘More accurate diagnosis, fewer antibiotic prescriptions’, ‘Non-pharmacologic treatment with additional health benefits’. See https://youtu.be/xHmJGS9n2I Earlier identification of a higher risk group in pneumonia |
| Press summary* | min 200, max 300 words (1-2 sentences per question) | How would you tell the world about your work? | 1) Lymphocyte count is strongly associated with mortality in pneumonia in primary care  
2) Earlier identification of high risk groups could lead to better diagnosis and treatment  
3) Lymphocyte counts are commonly measured as part of routine blood work and are readily available on many patients |
| Press release from institution | n/a | Please send any institutional/academic organisation press releases to Moira.Davies@rcgp.org.uk when available |

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| Multimedia (If applicable) | max 200 + images/multimedia files | Would you like your article to be considered for a video animation or infographic? Of so, please state: 1) What could be the single subject/focus of a visualisation of your article? 2) What are some highlights that would be relevant to visualise?, e.g. - findings that are surprising or unexpected - contrasts, e.g. between study groups or conditions, or proportions - visual motifs, symbols, diagrams, pictures, or videos (with subjects’ consent) Sketches and sample images can be uploaded to the submission system, and links can be added here. Articles with clear visual angles which are being considered for multimedia production will be contacted shortly after acceptance. | 1) The single picture would be figure 3 - I will attach with the email for ease. It’s a nice visualisation of increased risk. 2) |

If you have any queries please email journal@rcgp.org.uk
Prior lymphopenia is associated with mortality in primary care pneumonia: a cohort study.