sive metastases indicative of aggressive disease. In addition, there was evidence of colonic metastasis, a rare phenomenon in the setting of CCA (8), and one that has not been previously reported in LEL-CCA. Finally, although azathioprine is associated with EBV-positive lymphoproliferative disorders, neither it nor anti-TNF therapy has been shown to increase the risk of EBV-positive carcinoma (9,10).

In conclusion, we report a rare case of metastatic EBV-positive LEL-CCA in a young individual with IBD-PSC. This variant of CCA should be considered in the differential diagnosis for IBD-PSC patients with metastatic cancer and extensive intra-abdominal lymphadenopathy. Thorough investigation including imaging, histopathology, and endoscopic studies should be undertaken to establish the diagnosis.

CONFLICT OF INTEREST

Guarantor of the article: Karthik Ravi, MD.
Specific author contributions: First manuscript draft, collation of edits, and images: Tan; manuscript drafting and editing: Majumder; manuscript editing from oncologic perspective: Sridharan; manuscript editing from histopathologic perspective: Kerr and Graham; manuscript editing and supervision of project: Ravi. All authors read, edited, and approved the final draft submitted.
Financial support: None.
Potential competing interests: None.

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Proton-Pump Inhibitors and Fragility Fractures in Vulnerable Older Patients

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doi:10.1038/ajg.2016.584

To the Editor: Proton Pump Inhibitors (PPIs) taken for ≥1 year have been linked to increased fragility fracture (FF) risk, prompting the US FDA to issue a related warning. The oldest old (≥85) and patients with comorbidities may be at greater risk (1); however, little or no evidence has been available in these groups of vulnerable people. In this retrospective-matched cohort study with difference-in-difference methods, we investigated the 4-year FF risk in older patients (≥60) and patients with comorbidities.

We used the Clinical Practice Research Datalink, a database of primary care electronic medical records linked to hospital records. The sample included 86,469 patients receiving PPIs for ≥1 year and 86,469 age- and gender-matched controls, registered with a primary care practice in England between April 1997 and March 2014.

PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) were identified in the electronic prescribing data and analyzed as a class, regardless of dosage. The date of the first PPI prescription for the treated member of each matched pair was deemed the pair's index date.

FFs, were defined by hospitalization for new spine, hip, wrist, humerus, pelvis, ankle and rib fracture, coded using ICD-10. Patients with FFs within 3 months before their first PPI prescription were excluded, to avoid bias (2).

Cox's regressions were used to compare FF risk during the 4 years before (pre-treatment period) and after (treatment period) index date. According to the Prior Event Rate Ratio (PERR) approach (3), a difference-in-difference method, hazard ratios in the pre-treatment period were used to correct the treatment period hazard ratios. PERR was used to address both measured and unmeasured confounding, the latter being a major caveat in the interpretation of current evidence (4).

Results were stratified by age (60–74, 75–84, and ≥85) and comorbidity (Charlson comorbidity index, 0 and ≥1). Numbers needed to harm (NNHs) were also calculated (5). Subgroups were compared using confidence intervals since interactions cannot be tested using PERR.

The mean age was 71.9 (±7.9) years. FF rates in people aged ≥60 and those 60–74, 75–84, and ≥85 were 11.7, 7.3, 18.5, and 33 per 1000 person-years, respectively.

Differences at index date between treatment groups (**Table 1**) were reflected by higher hazard ratios in patients exposed to PPIs in both pretreatment and treatment

Table 1. Percent of selected characteristics at index date

Characteristic[a]	Controls *N*=86,469	Treated *N*=86,469
Age group		
60–74	66.1	66.1
75–84	27.7	27.7
85+	6.3	6.3
Gender (women)	56.4	56.4
Ethnicity		
White	60.2	79.9
Non-white	1.4	2.5
Not recorded/Undisclosed	38.5	17.5
Poorer socio-economic status (3rd–5th quintile of index of multiple deprivation)	50.3	52.2
Body mass index		
Underweight (<18.5 kg/m^2)	1	1
Normal (18.5–24.9 kg/m^2)	17.3	18.4
Overweight (25–29.9 kg/m^2)	20.4	25.8
Obese (≥30 kg/m^2)	12.7	18.1
Unrecorded	48.5	36.8
Smoking status		
Never smokers	44.6	41
Ex-smokers	17.6	21.9
Current smokers	28	32.6
Not recorded	9.8	4.4
Alcohol drinking		
Never/currently not	9	10.6
Current, known amount	42.2	47.2
Heavy	9.4	12
Current, unknown amount	0.9	1
Former	2.2	3
Undetermined	36.4	26.2
Charlson comorbidity index (≥1)	39.8	57.6
Falls (within a year before baseline)	11.6	16.6
Anaemia	2.7	7.7
Ischemic stroke	5.5	9.3
Coronary heart disease	10.5	20.1
Osteoporosis	3.6	6
Osteoarthritis	19.9	32.6
Gastroesophageal reflux disease	0.2	4.6
Vitamin D supplement	3.9	9
Corticosteroids	25.2	44.3
Oestrogen	2.2	4.4
Testosterone	0.1	0.1
Anti-thyroid drugs	0.2	0.3
Levothyroxine	6	8.6

[a]All differences (except for gender and age groups) between the PPI-treated and controls significant at $P<0.001$ (χ^2).

periods (**Figure 1**). Measured and unmeasured confounding has been addressed using PERR.

In the adjusted analysis (net estimates, **Figure 1**) across the studied age-range, patients receiving PPIs were at greater risk of FF than controls (PERR-adjusted Hazard Ratio: 1.27: 95%CI: 1.16–1.34) after accounting for prior differences in FF rates. The Hazard Ratio for PPI use in those aged ≥85 overlapped with that in younger groups and were similar in patients with and without comorbidity. Sensitivity analyses excluding people with corticosteroids co-prescription and their matched pairs showed similar results (HR: 1.23, 95%CI: 1.05–1.44).

Since the hazard estimates were similar in age and comorbidity subgroups, subgroup-specific NNHs were calculated by applying the full-sample risk estimate to subgroup-specific FF rates (5). The NNH for FF in all patients aged ≥60 was 121 (95%CI: 81 to 222) over 4 years. NNH in patients ≥85 (45, 30 to 81) was lower than that in ages 60–74 (207, 141 to 368) but similar in patients with and without comorbidity (data not shown).

This observational study, using a validated method to address unmeasured confounding, confirms an ~30% increased FF risk in older patients receiving PPIs for ≥1 year. Although there were similar excess risks in patients aged ≥85, given the higher absolute risk of FF in this group, only 45 patients need to be treated to harm one, suggesting that PPIs should be used with caution especially for symptomatic relief in this group. In the UK, the vast majority of people aged ≥60 receive free drug prescriptions and the ≥1 year over-the-counter PPI use is therefore limited and unlikely to bias our results.

CONFLICT OF INTEREST

Guarantor of the article: Alessandro Ble, MD.

Specific author contributions: Study concept and design, acquisition or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis and approved the final draft: Jan Zirk-Sadowski;

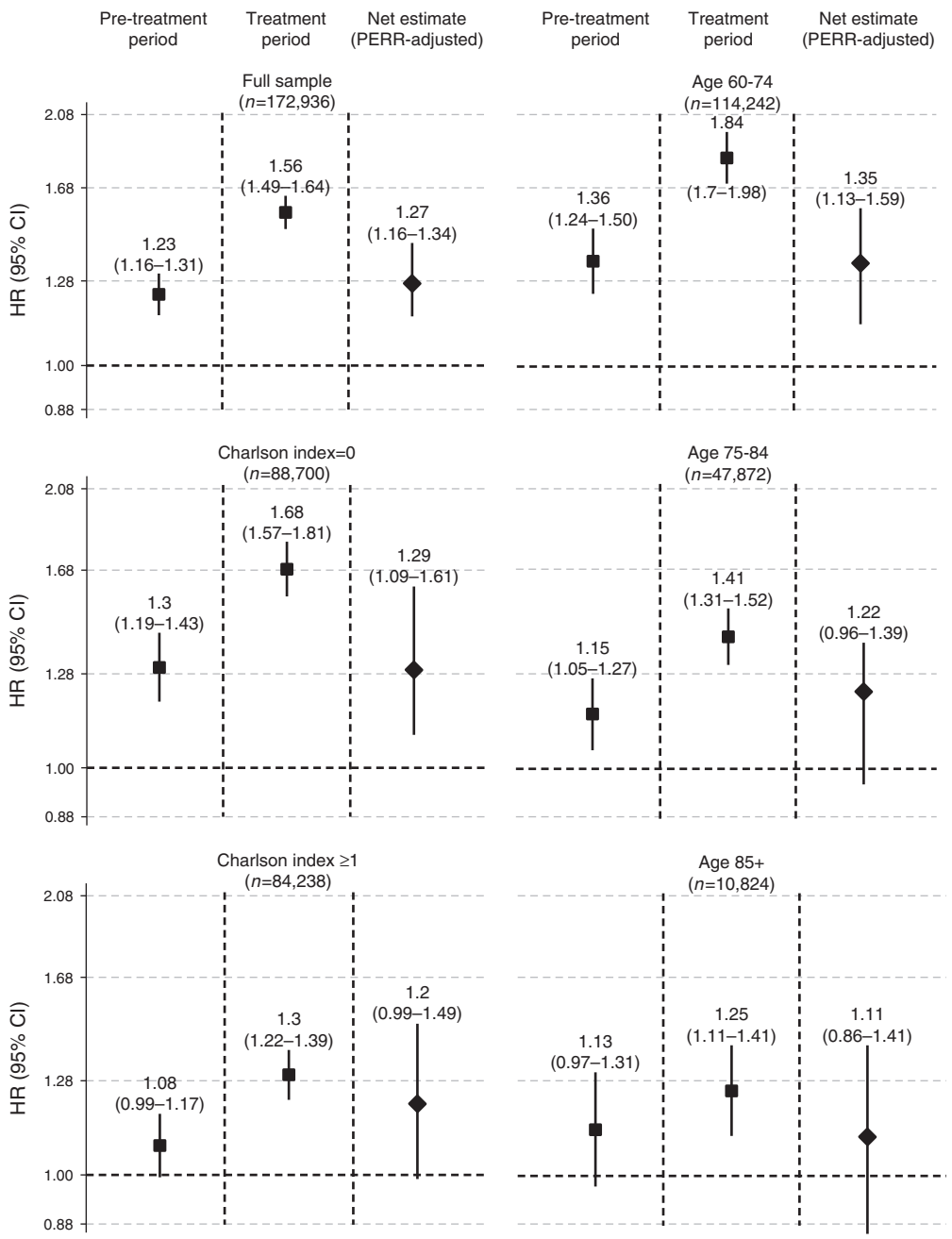

Figure 1. Hazard ratios for pre-treatment and treatment periods, and PERR-adjusted hazard ratios for the full sample and by comorbidity and age groups (log-scale). Confidence intervals for PERR analyses were calculated using bootstrapping techniques. 95%CI, 95% confidence interval; CCI, Charlson Comorbidity Index; HR, hazard ratio; $HR_{PERR}=HR_{Treatment\ period}/HR_{Pre\text{-}treatment\ period}$; PERR, Prior Event Rate Ratio.

Study concept and design, acquisition or interpretation of data, drafting of the manuscript and critical revision of the manuscript for important intellectual content: Jane A. Masoli; acquisition or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content and approved the final draft: David Strain; acquisition or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content and approved the final draft: Joao Delgado; acquisition or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content statistical analysis and approved the final draft: William Henley; acquisition or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content and approved the final draft: Willy Hamilton; Study concept and design, acquisition or interpretation of data, drafting of the manuscript, critical revision of the manuscript

for important intellectual content statistical analysis and approved the final draft:David Melzer; Study concept and design, acquisition or interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis and approved the final draft: Alessandro Ble. Dr Zirk-Sadowski and Dr Ble had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial support: This research is funded by the National Institute for Health Research (NIHR), grant number: PB-PG-0214-3309. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the UK Department of Health.

Potential competing interests: Alessandro Ble is a former employee of Pfizer (until November 2012). The remaining authors declare no conflict of interest.

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