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Improved survival for HIV infected patients with severe *Pneumocystis jirovecii* pneumonia is independent of highly active antiretroviral therapy

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Abstract

Background: Despite a decline in incidence of *Pneumocystis jirovecii* pneumonia (PCP), severe PCP continues to be a common cause of admission to the intensive care unit (ICU), where mortality remains high.
Objective: To describe outcome from intensive care for patients with PCP and to identify prognostic factors.
Methods: Retrospective cohort study of HIV-infected adults admitted to a university-affiliated hospital ICU between November 1990 and October 2005. Case-note review collected information on demographic variables, patient's receipt of prophylaxis and highly active antiretroviral therapy (HAART) and hospital course. The main outcome was one month mortality, either on the ICU or in hospital.
Results: Fifty-nine patients were admitted to the ICU on 60 occasions. Thirty four patients (57%) required mechanical ventilation (MV). Overall mortality was 53%. No patient received HAART before, or during ICU admission. In multivariate analysis factors associated with mortality were the year of diagnosis (pre-mid-1996 [mortality = 71%] compared with later [mortality = 34%]) ($p = 0.008$), patient's age ($p = 0.016$) and the need for MV and/or development of pneumothorax ($p = 0.031$). Mortality was not associated with patient's gender, ethnicity, prior receipt of sulpha prophylaxis, haemoglobin, serum albumin, CD4 count, PaO_2, A-a O_2 gradient, co-pathology in bronchoscopic lavage fluid, medical comorbidity, APACHE II score, or duration of MV.
Conclusions: Observed improved outcomes from severe PCP admitted to the ICU occurred in the absence of intervention with HAART and likely reflect general improvements in ICU management of respiratory failure and ARDS, rather than improvements in the management of PCP.

Introduction

Pneumocystis jirovecii pneumonia (PCP) continues to be a common opportunistic infection in individuals with HIV infection [1], and it remains a common indication for admission to the intensive care unit (ICU). Several studies have shown that between one quarter and one third of all ICU admissions of HIV infected patients are due to PCP [2][3][4]. Outcomes from mechanical ventilation for severe PCP have changed dramatically since the start of the AIDS pandemic. Before 1989 reports indicated that hospital survival rates were < 20% [5][6][7][8][9]. Based on this information many centres, including our own, did not refer HIV infected patients with severe PCP and respiratory failure to the ICU for mechanical ventilation. Later reports, in the late 1980s and early 1990s, showed hospital survival rates were higher, ranging from 40 -54% [10][11][12]. This improvement was ascribed to the use of adjunctive corticosteroids in severe PCP [10][12][13]. In the mid-to-late 1990s further reports suggested survival of patients with PCP and respiratory failure had not improved and was < 25%, reflecting a poor outcome in patients who had 'failed' adjuvant corticosteroids and who were admitted to ICU ≥ 5 days after starting specific anti-Pneumocystis therapy [9][12][13][14][15][16][17].

Several factors associated with poor outcome from PCP have been identified including patient's age [18,19], poor oxygenation at admission to hospital (based on PaO_2, or alveolar-arterial O_2 (A-a O_2) gradient) [7][20][21][22], elevated serum lactate dehydrogenase (LDH) enzyme levels [20][21][23] low haemoglobin [19][24], low serum albumin [4][20][25], presence of bacterial [21] or cytomegalovirus (CMV) [18] co-pathogens or neutrophilia in bronchoalveolar lavage (BAL) fluid [26], delay of ≥ 5 days in admission to ICU after starting specific anti-*Pneumocystis* therapy [12][25], high Acute Physiology and Chronic Health Evaluation (APACHE) II scores [3][25][27] and development of pneumothorax during mechanical ventilation [9][27]. Results from these studies are inconsistent as not all show these factors to have prognostic value. There is no scoring system with sufficient accuracy to enable identification of individuals for whom referral to ICU for mechanical ventilation would be futile.

One recent retrospective study from San Francisco General Hospital demonstrated improved survival from HIV-associated PCP in patients who either began highly active antiretroviral therapy (HAART) while on ICU, or who were receiving HAART before admission to ICU (survival = 63%) compared to those who did not receive HAART (survival = 25%) [28]. By contrast, acute deterioration has been described when HAART is commenced during treatment of severe PCP [29][30]. At our treatment centre HAART is not started during treatment of acute intercurrent opportunistic infections but our perception was that outcomes had steadily been improving in this patient group. We performed a retrospective study of all HIV infected patients with PCP admitted to our ICU from 1990 to the present, in order to document trends in outcome and survival and to identify prognostic factors associated with death.

Methods

Patients

Consecutive HIV infected adults admitted to the ICU at University College London Hospitals (UCLH) from November 1990 until October 2005 were identified. Prior to

this time HIV infected patients with severe PCP were not admitted to the ICU: instead they were managed on a specialist HIV/AIDS ward and were given respiratory support with continuous positive airways pressure (CPAP) delivered via a face mask [31]. All patients had microscopically confirmed PCP [32]. In 56 episodes PCP was diagnosed by bronchoscopy with BAL and four episodes were diagnosed at necropsy. Each patient had one ICU admission, apart from one female who had two admissions, in 1993 and 1995, the second of which lead to death. Patients in whom the diagnosis of PCP was made empirically [33] were excluded from the main part of the study, but limited information was collected for comparison purposes. Patients were identified from a manual and electronic search of hospital discharge summaries of HIV infected patients and cross referenced with the electronic ICU database and with the pathology department records. UCLH is a 936 bedded university-affiliated teaching hospital that provides inpatient care for HIV infected patients: there are 22 general ICU beds. The study was carried out with the approval of the University College London Hospitals Research Ethics Committee. The size of the study was not based on a power calculation.

Data collection

Demographic information recorded included age, gender, ethnicity, and risk factor for HIV acquisition, patient's awareness of their HIV serostatus at admission, previous history of PCP and receipt of PCP prophylaxis. The admission PaO_2 (breathing room air), A-a O_2 gradient, haemoglobin and serum albumin, CD4 count (on, or within one month before admission), presence of co-morbidity and evidence of co-pathogens in BAL fluid (bacterial infection or CMV) defined as previously described [32][34] were recorded. Serum LDH is not routinely measured in patients with PCP at out treatment centre. Data recorded on each patient's hospital course included treatment of PCP and whether treatment was changed because of drug failure. Treatment failure was defined as a need for change in therapy due to persistent fever or worsening hypoxaemia, with or without radiographic deterioration, occurring after a minimum of 5 days of primary therapy (including adjuvant corticosteroids), or a lack of improvement in oxygenation, chest radiograph, or clinical symptoms after ten days of primary therapy [35][36]. Hospital day of admission to ICU, APACHE II score [37] on day of ICU admission, duration of ICU stay, need for MV, development of pneumothorax (and whether pneumothorax occurred during MV) and outcome were also recorded. Outcome was described either as death or survival 4 weeks after completing treatment for PCP. Whether death occurred on ICU or elsewhere in the hospital was also recorded. Patients surviving ICU admission were followed up for three months.

Statistical analysis

Stata version 7.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis. A p value of < 0.05 was regarded as statistically significant. Univariate analyses were performed using a 2-tailed Fisher exact test for binary variables and a Mann-Whitney test for continuous variables to assess variables associated with survival. Only one patient with a pneumothorax was not mechanically ventilated, therefore we created a variable that accounted for both the need for MV and/or development of pneumothorax. Stepwise forward multivariate logistic regression was performed in order to determine variables (factors) predictive of poor outcome. The two episodes from one patient are treated in analysis as independent. Data presented are based on episodes.

Results

Fifty-nine HIV infected patients were admitted to the ICU with severe PCP on 60 occasions between November 1990 and October 2005. Overall mortality was 53%. Mortality before mid-1996 was 71% and thereafter was 34%. During this time period 328 patients had 367 episodes of microscopically confirmed PCP at this centre. A significantly higher ($p = 0.003$) proportion of patients with PCP were admitted to the ICU in the period 2002-2005 (43%, 13/38) than in the rest of the study period (14%, 47/329) (Figure 1).

Patients admitted to the ICU were predominantly men (87%); their main HIV risk factor was sex with other men (MSM) (67%) and their median (range) age was 36.5 (23 – 68) years (Table 1). A comparison of patients with PCP before mid-1996 (n = 31) and those presenting after this time (n = 29) showed patients had similar ages; median (range) = 41 (23 -68) years and 35 (26 – 68) years, respectively; $p = 0.66$. The majority were male, 94% (29/31) before mid-1996 and 79% (23/29) subsequently; $p = 0.14$. Patients were more likely to be MSM before mid-1996 (84%, 24/31) than later (48%, 14/29); $p = 0.006$.

Admission with PCP in the 59 patients represented the initial HIV diagnosis for 35 (58%) patients. None were receiving HAART on admission to hospital and none began this therapy while in the ICU: 51 (85%) were not receiving PCP prophylaxis prior to hospital admission. Patients generally had advanced HIV disease with a median [range] CD4 count of 30 [0-320] cells/μl. All but 3 patients had CD4 counts ≤ 200 cells/μl. In 57 (95%) episodes this was the first episode of PCP; in 3 (5%) it was the second episode. Thirty-four patients required MV (57%) and twelve developed a pneumothorax; in 11 (92%) of these pneumothorax occurred while being mechanically ventilated. Twenty-six patients (43%) did not require MV and instead received respiratory support including CPAP.

Primary therapy was co-trimoxazole in 56 (93%) episodes, clindamycin with primaquine in 3 (5%) and intravenous pentamidine in 1 (2%): 56 (93%) also received adjuvant corticosteroids. At the time of admission to the ICU 6 (10%) patients were already receiving second line therapy due to failure of first line treatment. Co-pathology was identified in the BAL fluid of 12 (20%) patients, namely *Streptococcus pneumoniae* (3), *Staphylococcus aureus* (2 [one also had CMV]), *Pseudomonas aeruginosa* (2) and CMV alone (5). Twelve (20%) patients had co-morbidities; cryptococcal infection (4), heart failure/cardiomyopathy (2) and histoplasmosis, recent cerebrovascular accident, tuberculosis, hypothyroidism, kyphoscoliosis and acute renal failure in one patient each. Of 56 episodes of PCP diagnosed by bronchoscopy and BAL, 16 patients (18%) were admitted to the ICU within 24h of the procedure; six of these patients required MV on admission to the ICU, 10 did not. Disease severity in these 16 patients, as determined by PaO_2, (median [range] PaO_2 = 7.7 [3.9 -13.6] kPa) was no different to the rest of the group. Overall 32 (53%) patients did not survive their episode of PCP. The majority of deaths were due to progressive respiratory failure. Of those dying, 26 died on the ICU and six died on the specialist HIV/AIDS ward following discharge from the ICU.

In univariate analysis the only factors significantly associated with mortality were the year of diagnosis of PCP (pre-mid 1996 vs later), age and the need for MV and/or development of pneumothorax (Table 1). None of gender, ethnicity, HIV risk factors, lack of awareness of HIV status, a prior history of PCP, receipt of PCP prophylaxis, haemoglobin, serum albumin and CD4 count, PaO_2, A-a O_2 gradient, co-pathology in BAL fluid, medical co-morbidity, APACHE II score, or duration of MV were significantly associated with mortality. However, there was some evidence of an association with serum albumin and lack of awareness of HIV status. In multivariate analysis (Table 2) the year of diagnosis of PCP, age and the need for MV and/or development of pneumothorax remained significantly associated with mortality. The severity of microbiologically confirmed PCP, measured by admission PaO_2, throughout the study period, both in those admitted to ICU and in all those with PCP is shown in Table 3. A comparison of patients presenting after mid-1996 with those presenting before revealed a significantly lower PaO_2 in both those admitted to the ICU ($p = 0.003$) and overall ($p < 0.001$). Among survivors, duration of ICU stay was 1-17 (3) days [range (median)] before mid-1996 and was 1-34 (11) days subsequently ($p = 0.92$).

When longer term survival (at three months) was considered, a marked decline in mortality over time was also identified. Mortality before mid-1996 was 74% (23/31) and 38% (11/29) subsequently; $p = 0.009$. Restricting analysis to only those who were mechanically ventilated, a reduction in one month mortality from 81% (13/16) before mid-1996, to 50% (9/18) thereafter was observed. This was not statistically significant; $p = 0.08$. The rate of pneumothoraces in mechanically ventilated patients was 43% (7/16) before mid-1996 and 28% (5/18) subsequently; $p = 0.475$.

Twenty-four additional patients with ‘empirically treated’ PCP were admitted to the ICU during the study period. Among this group mortality also declined markedly over time ($p = 0.01$), being 91% (10/11) before mid-1996, and 38% (5/13) thereafter. This mortality rate overall (63%) was somewhat higher than in those with microscopically confirmed PCP (53%); $p = 0.48$.

Discussion

This study demonstrates an improved survival for HIV infected patients with PCP who require admission to the ICU. Although overall mortality was 53%, mortality rates at this treatment centre have fallen since mid-1996. Independent predictors of mortality in this study were the year of diagnosis of PCP, the patient’s age and the need for MV and/or development of pneumothorax. In multivariate analysis these factors remained significant. Overall survival from PCP has improved during the last two decades [38][39]. Morris et al [28] suggested that improved survival among HIV infected patients with severe PCP who were admitted to the ICU was related to patient’s receipt of HAART, which became available in the United Kingdom in mid-1996. In our institution, mortality from severe PCP requiring admission to the ICU fell, from 71% before mid-1996 to 34% subsequently, despite the fact that no patient received HAART prior to or during admission to the ICU. These survival figures are similar to those reported by Morris et al [28]. In our study the observed improved survival cannot be ascribed to HAART.

Over the last decade there have been several changes in the ICU management of patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which have positively impacted on survival [40][41]. In particular, the use of lower tidal volumes and higher levels of positive end-expiratory pressure for MV are associated with better outcomes [40][41]. With these interventions survival from ARDS has improved from 41-52% before 1991 to 60-75% in 1993 and subsequently [40][41]. This centre's strategy for management of mechanically ventilated patients with ALI/ARDS changed soon after publication of data from Hickling et al, which showed a reduced mortality rate if low tidal volume ventilation with permissive hypercapnia was used [42]. Thus, by early 1996 our centre allowed mechanically ventilated patients with ALI/ARDS to tolerate greater levels of hypoxaemia and permissive hypercapnia. Additionally, mechanically ventilated patients were less frequently paralysed and less iv fluid was administered to critically ill patients than previously. This suggests that the observed improvement in survival from severe PCP reflects improvements in ICU management of severe respiratory failure, rather than changes in specific management of PCP.

The introduction and uptake of HAART in mid-1996 was associated with a marked reduction in AIDS events and mortality [43]. This was accompanied by a changed perception among clinicians caring for patients with HIV infection such that they were more likely to refer to the ICU patients with severe PCP, as demonstrated by results from the last quarter of this study, where a greater proportion of patients with PCP were admitted to the ICU. Throughout the study period there were no changes in clinical practice, as bronchoscopy with BAL was used as the exclusive diagnostic modality and no transbronchial biopsies (with the attendant risk of pneumothorax) nor open lung biopsies were performed; first-line therapy was co-trimoxazole, regardless of disease severity and adjuvant corticosteroids had been introduced in late 1989 for those with $PaO_2 < 9.3$ kPa. However, among those surviving severe PCP there was a trend, which did not reach statistical significance, for the duration of ICU stay to be longer after mid-1996, perhaps reflecting treatment optimism among clinicians.

This study has two weaknesses. Firstly, only patients with microscopically confirmed PCP were included in the analysis. Those with a presumptive diagnosis and who were treated empirically were excluded [33]. Many of these latter patients were too sick to bronchoscope and may/may not have had PCP. No necropsy was performed in these patients and so uncertainty remains regarding their diagnosis. Secondly, the current study population was small and is not based on a power calculation, yet is comparable in size to the majority of studies of PCP in the ICU between 1981 and 2003 and which have previously identified factors which have prognostic significance[3][4][7][9][12][14][15][16][17][18][19][20][21] [22] [23][24][25][26][27]. Nevertheless, interpretation of associations which are not statistically significant requires caution.

The suggestion that the observed improved prognosis in this study results from patients being more likely to be younger in recent years, to present with milder disease and with a previous diagnosis of HIV is not supported by the study findings. No differences were seen over time in patient's age, prior knowledge of their HIV serostatus, CD4 count and haemoglobin [both surrogates of advanced HIV infection], or median PaO_2 at presentation. A majority of patients throughout the study presented with late stage HIV infection and PCP as their AIDS-defining events. These data

contrast with previous reports, which have identified that these prognostic factors are associated with death from PCP [3][4][7][9][12][13][14][15][16][17][18][19][20][21][22][23][24][215][26][27]. Two previous studies showed patient's prior receipt of PCP prophylaxis was associated with a poor outcome from severe PCP [44][45], and was ascribed to acquired co-trimoxazole resistance [45]. By contrast, we were unable to demonstrate an association between patient's prior receipt of sulpha prophylaxis and death, however only nine (15%) patients had received co-trimoxazole prior to presentation with PCP.

We identified no difference in outcome from severe PCP, regardless of duration of specific therapy before admission to the ICU, as reported previously [44]. These data contrast with other reports which hypothesized that if a patient deteriorated within 5 days of starting anti-*Pneumocystis* therapy deterioration was occurring before adjuvant corticosteroids had become effective, whereas if deterioration occurred ≥ 5 or more days after starting therapy patients in who adjunctive corticosteroids had not worked and who were deteriorating despite maximal therapy had been selected [5][25]. Our data suggest that referral to ICU for management of severe PCP is appropriate even in patients deteriorating after > 5 days of maximal therapy. By contrast with a previous study, that demonstrated better ICU outcomes for patients with PCP who deteriorated immediately after bronchoscopy and BAL [7], in the present study 16 (18%) patients admitted to ICU within 24h of BAL had similar outcomes and showed no differences in PaO_2, compared with the group as a whole.

The data from this study show improved survival from severe PCP in recent years in the context of the advent of HAART and support early referral to the ICU of patients with severe PCP for management of respiratory failure. We failed to identify specific factors associated with poor outcome, such as patients failing first-line therapy, or prolonged interval between hospitalization and ICU admission, which would preclude referral to the ICU for management. The observed improvements in outcome from ICU for patients with severe PCP occurred in the absence of intervention with HAART and probably reflect general improvements in ICU management of respiratory failure and ARDS, rather than to improvements in management of PCP *per se*.

Conflict of interest: Dr RF Miller is Co-Editor and Dr A Copas is Associate Editor of *Sexually Transmitted Infections*, part of the BMJ Publishing Group.

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Table 1. Characteristics of 60 episodes of microbiologically confirmed PCP admitted to the intensive care unit according to survival

Characteristic	Survivors N = 28 n (%)	Non-survivors N = 32 n (%)	Overall N = 60 n (%)	P value
Gender				
Male	23 (82)	29 (91)	52 (87)	
Female	5 (8)	2 (9)	8 (13)	0.454
Race/ethnicity				
white	24 (86)	22 (69)	46 (77)	
Other	4 (14)	10 (31)	14 (23)	0.214
Year of diagnosis				
Pre middle 1996	9 (32)	22 (69)	31 (52)	
Post middle 1996	19 (68)	10 (31)	29 (48)	0.009
HIV risk factor				
men who have sex with men	18 (64)	22 (69)	40 (67)	
heterosexual	10 (36)	10 (31)	20 (33)	0.787
Known to be HIV infected prior to presentation with PCP				
Yes	8 (29)	17 (53)	25 (42)	
No	20 (71)	15 (47)	35 (58)	0.069
Age, years, median (range)	32.5 (23-60)	41.5 (25-68)	36.5 (23-68)	0.025
Prior history of PCP				
Yes	0 (0)	3 (9)	3 (5)	
No	28 (100)	29 (91)	57 (95)	0.241
Receipt of PCP prophylaxis				
Yes	2 (7)	7 (22)	9 (15)	
No	26 (93)	25 (78)	57 (95)	0.155
Laboratory results				
CD4 cells (x 10^6/l), median (range)	35 (0-320)	30 (0-100)	30(0-320)	0.515
Admission PaO_2, breathing room air (kPa), median (range)	7.0 (4.0-13.6)	7.8 (3.9 - 11.3)	7.6 (3.9 – 13.6)	0.583
Admission A-a O_2 gradient (kPa)	7.4 (1.6 – 10.8)	7.3 (2.4 – 10.6)	7.3 (1.6 – 10.6)	0.699
Haemoglobin (g/dl), mean (SD)	11.4 (1.87)	10.8 (1.49)	11.1 (1.69)	0.176
Serum albumin (g/l), mean (SD)	27.4 (5.97)	24.6 (5.42)	26.0 (5.81)	0.071
APACHE II score, mean (SD)	15.1 (4.08)	16.1 (6.52)	15.6 (5.49)	0.522
Complications				
Admission to ICU				
≤5 days after hospital admission	17 (61)	19 (59)	36 (60)	
>5days after hospital admission	11 (39)	13 (41)	24 (40)	0.563
Treatment failure at admission to ICU	2 (7)	4 (13)	6 (10)	
Yes	25 (93)	28 (87)	54 (90)	0.678
No				

Medical co-morbidity	3 (11)	9 (28)	12 (20)	
Yes	25 (89)	23 (72)	48 (80)	0.115
No				
CMV infection in BAL fluid	3 (11)	3 (9)	6 (11)	
Yes	25 (89)	25 (91)*	50 (89)	1.00
No				
Bacterial infection in BAL fluid				
Yes	3 (11)	4 (14)	7 (12)	
No	25 (89)	24 (86)*	49 (88)	1.00
Medical co-morbidity, CMV or bacterial infection in BAL fluid				
Yes	9 (32)	14 (44)	23 (38)	
No	19 (68)	18 (56)	37 (62)	0.430
Mechanical ventilation				
Yes	12 (43)	22 (69)	34 (57)	
No	16 (57)	10 (31)	26 (43)	0.067
Duration of mechanical ventilation, days				
median (range)	8 (1-28)	11.5 (1-75)	9.5 (1-75)	0.539
Pneumothorax				
Yes	4 (14)	8 (25)	12 (20)	
No	24 (86)	24 (75)	48 (80)	0.349
Mechanical ventilation and/or pneumothorax				
Yes	12 (43)	23 (72)	35 (58)	
No	16 (57)	9 (28)	25 (42)	0.036
Survival				
Died in ICU	0 (0)	26 (81)	26 (43)	
Died in hospital	0 (0)	6 (19)	6 (10)	
Survived to hospital discharge	28 (100)	0 (0)	28 (47)	NA

Key: PCP = *Pneumocystis jirovecii* pneumonia, APACHE = Acute Physiology and Chronic Health Evaluation, ICU = intensive care unit, CMV = cytomegalovirus, BAL = bronchoscopic alveolar lavage fluid, * = 4 patients were diagnosed at necropsy, NA = not applicable.

Table 2. Multivariate analysis of factors associated with mortality

Characteristic	**Odds Ratio [95% CI]**	**P value**
Age (log* years)	19.76 [1.74 - 224.34]	0.016
Year of PCP diagnosis (Post mid-1996)	0.14 [0.03 - 0.59]	0.008
Mechanical ventilation and/or pneumothorax	5.18 [1.16 - 23.15]	0.031

Key: * = natural log

Table 3. Admission oxygenation ($Pa0_2$, breathing room air), for all patients with microbiologically confirmed PCP and for those admitted to ICU with microbiologically confirmed PCP

Study period/ patient group	Admission $Pa0_2$ (kPa, breathing room air) [median (range)]*
1990-1993	
ICU PCP (n=14)	7.9 (3.9 -13.1)
All PCP (n=137)	9.4 (3.9 -13.2)
1994-1997	
ICU PCP (n=28)	7.7 (4.8 – 13.6)
All PCP (n=148)	9.4 (5.0 -13.6)
1998-2001	
ICU PCP (n=5)	6.2 (4.0 -10.1)
All PCP (n=44)	9.3 (4.0 -13.2)
2002-2005	
ICU PCP (n=13)	6.9 (5.2 - 8.7)
All PCP (n=38)	7.9 (5.2 – 11.4)

Key: * = in a comparison of patients before mid-1996 and those presenting subsequently, PaO_2 was lower in those admitted to the ICU ($p = 0.003$) and overall ($p < 0.001$).

Figure 1. Number of cases of microscopically confirmed *Pneumocystis jirovecii* pneumonia (PCP) (red bars) diagnosed at University College London Hospitals by year and number of cases of microscopically confirmed PCP who were admitted to the ICU (green bars)