Abstract

**Background:** The existence of COPD and heart failure in elderly population adds additional morbidity and mortality risk than if those with only one of the two comorbidities. The aim of the current meta-analysis was to explore the effect of COPD on heart failure patient in terms of all-cause mortality, cardiac mortality and recurrent heart failure hospitalization.

**Methods and results:** A comprehensive search of PubMed, MEDLINE, Embase and Cochrane was conducted until August 2017. The total standardized mean difference, with 95% (CI), was estimated for fixed and random effects models to present "pooled effect" for continuous outcomes (mean ± standard deviation or median ± interquartile range) & categorical outcomes (Odds risk OR). Statistical heterogeneity among studies was assessed with Cochran’s Q test and the $I^2$ statistic. A total of 15 observational studies were analyzed. COPD and heart failure patients have higher: short term (in hospital, 1-3 months) ($P=0.009$, 0.0006 respectively), long term all-cause mortality (1& 2-5 years) ($P=0.00001$, 0.04 respectively), long term cardiac mortality ($P=0.02$) and more frequent hospitalization for heart failure ($P=0.002$). GOLD stage II-IV COPD had higher long-term all-cause mortality ($P<0.0001$) but not long-term cardiac mortality ($P=NS$). Beta blockers treatments appear to decrease all-cause mortality in COPD with heart failure ($P <0.0001$).

**Conclusion:** Heart failure patients with COPD have frequent heart failure hospitalization, higher long-term cardiac mortality, short- and long-term all-cause mortality that is more evident in advanced stage of COPD. Beta blockers use appear to be safe and decrease mortality in these patients.

Introduction

The co-occurrence of heart failure (HF) and chronic obstructive pulmonary disease (COPD) that share common clinical presentation and risk factors is common in the elderly population, such overlap makes the diagnosis of COPD in HF and vice versa challenging [1,2].

The existence of these clinical syndromes in elderly population adds additional morbidity and mortality risk than if those with only one of these diseases [3]. Furthermore, it will add dilemma to recognition of each when these disorders exist and leads to over diagnosis of heart failure in COPD patient or under diagnosis of COPD in heart failure patients [4]. Treatment interaction, the more complex issue is that the treatment of one may adversely affect the other [5], as bronchodilator may cause tachycardia and may precipitate heart failure furthermore beta blockers and diuretics may adversely affect COPD.

The above 2 clinical presentation has not analyzed systematically, with the presence of only observational studies that supply both cardiologist and internist with inconsistent information. We choose to systematically analyze the available research article, so we can reach final conclusion about the morbidity and mortality interaction between these conditions when heart failure patient with COPD presented with acute exacerbation.

The aim of the current meta-analysis was to explore the effect of COPD on heart failure patient in term of short- and long-term all-cause mortality and cardiac mortality and the effect of COPD on recurrent heart failure hospitalization.

Methods

**Search strategy & data collection**

A comprehensive search of PubMed, MEDLINE, Embase and Cochrane was conducted until August 2017, using combination of keywords; heart failure, COPD, all-cause mortality and cardiac mortality recurrent heart failure hospitalization. Along with available studies electronic search was done for abstracts, conference proceedings, unpublished and observational studies. References cited in the studies were reviewed for
additional information. The flow diagram shown in Figure 1, the search strategy yields 15 observational studies that met the study criteria.  

Criteria for study selection and qualitative assessment

The inclusion and exclusion criteria for the studies in the current meta-analysis are shown in Figure 2. Data regarding publication status, study design, patient-related characteristics, treatment regimens, outcome methods and results was extracted according to the standard protocol independently by 2 individual researchers. Any conflicts or incongruities were resolved by mutual agreement.

Clinical end points studied

The clinical endpoints that were analyzed in this meta-analysis are short- and long-term all-cause mortality, early and late cardiac mortality in all COPD patient and in subgroups as per COPD GOLD stages, recurrent heart failure hospitalization and the effect of B blocker treatment on all-cause mortality.

Statistical analysis

Review manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for the analysis. The total standardized mean difference (SMD), with 95% confidence interval (CI), was estimated for fixed and random effects models to present “pooled effect” for continuous outcomes (mean ± standard deviation or median ± interquartile range) & categorical outcomes (Odds risk OR). Statistical heterogeneity among studies was assessed with Cochran’s Q test and the I2 statistic. The studies were considered statistical heterogeneous if p < 0.05 and I² ≥ 50% [6,7]. A random effect model was used for analysis to determine the heterogeneity, and fixed effect model was used in case of homogeneity. Statistical significance value was set at 0.05. Processing of the data and reporting of results were performed according to accepted principles of systemic review and meta-analysis. In order to assess potential publication bias, or “small-study effect”, we used the funnel plot, which provides a good visual evaluation of sampling bias.

Results

A total of 15 observational studies [8–22], were identified, the baseline clinical characteristics of the patients included are shown in Table 1, Males were the predominant gender in these studies with the mean age shown being above 65 years of age with similar rate of CAD hypertension and dyslipidemia.

Patients with COPD and heart failure have higher short term (in-hospital, 1-3 months) (P=0.009, 0.0006 respectively, and long-term mortality (1 year, 2-5 years) (P=0.00001 for both) with moderate heterogeneity between the included studies) Figure 3.

The short-term cardiac mortality appears to be non-significantly (P=0.07) higher in COPD patients while the long-term cardiac mortality appears to be significantly higher (P=0.02) in COPD patient with heart failure with moderate heterogeneity between the included studies Figure 4.

COPD patient with heart failure have more frequent hospitalization for heart failure (P=0.002) with mild heterogeneity between the included studies Figure 5.

The heterogeneity of all the variable analyzed is shown in Funnel plots in Figure 6.

Patient with advanced stage [11,13,19], of COPD i.e. GOLD stage II–IV when compared to GOLD 0–I and non-COPD had higher long-term all-cause mortality (P<0.0001) [11,19], but not long-term cardiac mortality (P=NS). Figure 7 A,B.

Beta blockers treatments appear to decrease all-cause mortality [8,10,11], in COPD with heart failure as it does with non-COPD with heart failure (P <0.0001) Figure 7 C.

The multivariate analysis of the all-cause mortality predictors was shown in Table 1. The age, diabetes, COPD stage, low ejection fraction, and impaired renal function were the most frequent predictors in the included studies Figure 8.

Discussion

Heart failure and COPD as combined comorbidities presents a great diagnostics and therapeutic challenges, because both conditions share features such as; presentation in advanced age, common symptoms of dyspnea and smoking as a risk factor, in addition to that, treatment of one condition may
Table 1: Baseline clinical characteristics of the included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design/ period</th>
<th>Patients COPD vs. Non COPD</th>
<th>Age COPD vs. Non COPD</th>
<th>Male COPD vs. Non COPD</th>
<th>DM COPD vs. No COPD</th>
<th>Hypertension COPD vs. Non COPD</th>
<th>Dyslipidemia COPD vs. Non COPD</th>
<th>History of CAD COPD vs. Non COPD</th>
<th>Smoking History COPD vs. Non COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rothnie KJ 2015 / UK</td>
<td>Retrospective Observational 2003-2013</td>
<td>34019 vs. 266142</td>
<td>&gt; 60 years 77% vs. 66%</td>
<td>62% vs. 67%</td>
<td>16% vs. 15%</td>
<td>45% vs. 44.3%</td>
<td>27% vs. 28%</td>
<td>22% vs. 16%</td>
<td>43% vs. 34%</td>
</tr>
<tr>
<td>Polkutina OM 2015/Russia</td>
<td>Retrospective study from Jan – Dec 2008</td>
<td>65 vs. 464</td>
<td>67 (56.75) vs. 69 (55.72)</td>
<td>75% vs. 63%</td>
<td>14% vs. 20%</td>
<td>NR</td>
<td>NR</td>
<td>34% vs. 26%</td>
<td>54% vs. 41%</td>
</tr>
<tr>
<td>Andell P 2014 / Sweden</td>
<td>Retrospective analysis SWEDENHEART registry 2005-2010</td>
<td>4867 vs. 76324</td>
<td>75±9 vs. 70±13</td>
<td>54% vs. 64%</td>
<td>20% vs. 19%</td>
<td>32% vs. 20%</td>
<td>NR</td>
<td>14% vs. 8%</td>
<td>33% vs. 22%</td>
</tr>
<tr>
<td>Campo G 2013 / Italy</td>
<td>Retrospective analysis of REAL registry 2003-2009</td>
<td>2032 vs. 9086</td>
<td>70±12 vs. 65±13</td>
<td>66% vs. 74%</td>
<td>22% vs. 21%</td>
<td>70% vs. 61%</td>
<td>47% vs. 48%</td>
<td>17% vs. 14%</td>
<td>24% vs. 27%</td>
</tr>
<tr>
<td>Lazzieri C 2013/ Italy</td>
<td>Prospective 2005-2009</td>
<td>71 vs. 747</td>
<td>74(69–81) vs. 67 (58–76)</td>
<td>66% vs. 73%</td>
<td>34% vs. 27%</td>
<td>63% vs. 53%</td>
<td>NR</td>
<td>21% vs. 13%</td>
<td>76% vs. 62%</td>
</tr>
<tr>
<td>Sung PH 2013/ Taiwan</td>
<td>Prospective observational 2002-2011</td>
<td>124 vs. 1430</td>
<td>68.5±9.9 vs. 60.9 ± 12.6</td>
<td>85% vs. 81%</td>
<td>32% vs. 36%</td>
<td>55% vs. 56%</td>
<td>39% vs. 42%</td>
<td>4.8% vs. 4.4%</td>
<td>37% vs. 35%</td>
</tr>
<tr>
<td>Enriquez JR 2013 / USA</td>
<td>Retrospective analysis of ACTION registry-GWTG 2008-2010</td>
<td>22624 vs. 136266</td>
<td>68 vs. 63</td>
<td>58% vs. 66%</td>
<td>39% vs. 29%</td>
<td>82% vs. 71%</td>
<td>67% vs. 59%</td>
<td>36% vs. 23%</td>
<td>46% vs. 34%</td>
</tr>
<tr>
<td>Stefan MS 2012 / USA</td>
<td>Retrospective analysis WHA study</td>
<td>1080 vs. 5210</td>
<td>74±70</td>
<td>52% vs. 57%</td>
<td>37% vs. 32%</td>
<td>73% vs. 69%</td>
<td>NR</td>
<td>NR</td>
<td>27% vs. 20%</td>
</tr>
<tr>
<td>Quint JK 2011 / UK*</td>
<td>Retrospective Observational 2003-2008 MINAP and GPRD records</td>
<td>968 vs. 7097</td>
<td>NR</td>
<td>NR</td>
<td>48% vs. 40%</td>
<td>64% vs. 49%</td>
<td>39% vs. 31%</td>
<td>34.8% vs. 23.8%</td>
<td>39% vs. 36%</td>
</tr>
<tr>
<td>Hadi A 2010/ Middle Eastern countries</td>
<td>Retrospective analysis of prospectively collected data GulfTrace registry 2007</td>
<td>434 vs. 7733</td>
<td>64 vs. 55</td>
<td>NR</td>
<td>48% vs. 40%</td>
<td>64% vs. 49%</td>
<td>39% vs. 31%</td>
<td>34.8% vs. 23.8%</td>
<td>39% vs. 36%</td>
</tr>
<tr>
<td>Dziewierz A 2010/ Poland</td>
<td>Retrospective analysis of prospectively collected data Krakow ACS registry 2005 &amp; 2006</td>
<td>81 vs. 633</td>
<td>71.8±10.7 vs. 67.9±12.9</td>
<td>62% vs. 60%</td>
<td>23% vs. 23%</td>
<td>76% vs. 71%</td>
<td>37% vs. 47%</td>
<td>35% vs. 29%</td>
<td>41% vs. 32%</td>
</tr>
<tr>
<td>Bursi F 2010/ USA</td>
<td>Retrospective study Rochester Epidemiology Project 1979-2007</td>
<td>415 vs. 3023</td>
<td>73±11 vs. 67 ± 15</td>
<td>59% vs. 57%</td>
<td>23% vs. 21%</td>
<td>68% vs. 57%</td>
<td>43% vs. 39%</td>
<td>NR</td>
<td>35% vs. 26%</td>
</tr>
<tr>
<td>Wakabayashi K 2010/USA</td>
<td>Prospective study 1999-2008</td>
<td>365 vs. 2884</td>
<td>66.2±13.6 vs. 60.7±13.8</td>
<td>59% vs. 68%</td>
<td>36% vs. 29%</td>
<td>87% vs. 80%</td>
<td>85% vs. 83%</td>
<td>NR</td>
<td>40% vs. 37%</td>
</tr>
<tr>
<td>Hawkins NM 2009 Multinational</td>
<td>Retrospective analysis of VALIANT trial in 24 countries</td>
<td>1258 vs. 13445</td>
<td>68.1±9.9 vs. 64.5 ± 11.9</td>
<td>71% vs. 68%</td>
<td>26% vs. 23%</td>
<td>58% vs. 55%</td>
<td>36% vs. 29%</td>
<td>40% vs. 27%</td>
<td>42% vs. 31%</td>
</tr>
<tr>
<td>Rha SW 2009/ Korea*</td>
<td>Retrospective analysis of KAMIR registry 2005-2007</td>
<td>192 vs. 192</td>
<td>71.74±9.97 vs. 63.04±12.66</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>28.4% vs. 14.8%</td>
<td></td>
</tr>
<tr>
<td>Salisbury AC 2007 / USA</td>
<td>Retrospective analysis PREMIER registry 2003-2004</td>
<td>387 vs. 2094</td>
<td>64.5±12.4 vs. 60.1±13</td>
<td>62% vs. 68%</td>
<td>37% vs. 27%</td>
<td>68% vs. 63%</td>
<td>50% vs. 49%</td>
<td>30% vs. 20%</td>
<td>38% vs. 33%</td>
</tr>
<tr>
<td>Kjellor K 2003 /Denmark</td>
<td>Retrospective analysis of TRACE study 1990-1992</td>
<td>765 vs. 5904</td>
<td>70.5 vs. 68.2</td>
<td>68% vs. 67%</td>
<td>11% vs. 11%</td>
<td>18% vs. 23%</td>
<td>NR</td>
<td>25% vs. 23%</td>
<td>60% vs. 50%</td>
</tr>
<tr>
<td>Behar S 1992/ Israel</td>
<td>Retrospective analysis of SPRINT study 1981-1983</td>
<td>406 vs. 5433</td>
<td>66.8±9.7 vs. 62.7±10.8</td>
<td>79% vs. 73%</td>
<td>16% vs. 21%</td>
<td>37% vs. 40%</td>
<td>NR</td>
<td>29% vs. 24%</td>
<td>44% vs. 31%</td>
</tr>
</tbody>
</table>


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affects the other [1]. Unfortunately, this issue has not been studied systematically in randomized stream and even forgotten in major clinical trials. To the best of our knowledge this the first meta-analysis that explored the impact of COPD in heart failure patient. The absence of randomized trial makes the final result biased in many aspects. As we can see from the current analysis, few conclusions have been withdrawn:
First: The presence of COPD adds an increased risk of both short and long-term all-cause and long-term cardiac mortality in period of the follow up of the included studies which appear to be satisfactory in most of the studies that reach up to 5 years.

Second: Heart failure exacerbation on the background of COPD may be explained by many mechanisms; the low-grade inflammation, underuse of $\beta$-blockers, and adverse CV effects of bronchodilators [14,15]. The increased hospitalization rates in patients with HF and COPD may also be related to improvement in HF prognosis with contemporary therapies i.e. increase heart failure population. Alternatively, the improved survival of patients with HF and COPD, there is a larger population at risk for hospitalization.

Third: The severity of COPD appears to be directly proportional to the heart failure all-cause mortality and cardiac mortality and it appear that heart failure patient with advanced COPD i.e. GOLD stage $\geq$ II die from non-cardiac causes that related to associated comorbidities like diabetes and renal failure and advanced age as shown the mortality predictors in Table 1, though the mortality predictors were assessed only in few studies.

Fourth: Treatment of HF as per heart failure guidelines, necessitate the addition of beta blockers even in COPD patients, because there is no evidence that HF should be treated
Figure 8: Funnel plots.

Strength and limitations

The strength of this research is that it is the first meta-analysis done in this field of heart failure patients with COPD who presented acutely or chronically. The current meta-analysis result was extracted from observational studies most of which are retrospective analysis of major heart failure registries that can result in publication bias. In addition, the definition and staging of COPD was not available in many studies and that patient were considered to have COPD as per medical record and no spirometry done in these studies (only one prospective study included), the low number of patients included explore the need for large study that can achieve statistical power. The conclusion regarding B blockers in heat failure patient with COPD need to be interpreted carefully as this include relatively small number of patients from few retrospective studies though one of which was retrospective analysis of major heart failure registry, again necessitate the need for a large randomized controlled trial in this field.

Conclusion

Heart failure patient with COPD appear to have more frequent heart failure hospitalization, higher long-term cardiac mortality, short- and long-term all-cause mortality and this more apparent in advanced stages of COPD reflect the synergistic effect of both comorbidities. Beta blockers use appear to be safe as it decreases mortality in these patients.

References


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