**Abstract**

Patients who die within two years of oesophagectomy are more likely to have been smoking at the time of their operation, or to have developed ARDS or a surgical complication in the immediate post-op period.

<table>
<thead>
<tr>
<th>Died within 2 years</th>
<th>Survived 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 26)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td>ARDS – n (%)</td>
<td>11 (42)</td>
</tr>
<tr>
<td>Surgical Complication – n (%)</td>
<td>13 (50)</td>
</tr>
<tr>
<td>Current Smoker – n (%)</td>
<td>10 (41)</td>
</tr>
<tr>
<td>Median Pack Years</td>
<td>33</td>
</tr>
</tbody>
</table>

**REFERENCES**


**S98**

A NOVEL HUMAN MODEL TO STUDY ALVEOLAR INJURY AND REPAIR

Alçada, JP Nag-Blichfeldt, AG Proudfoot, MJD Griffiths, CH Dean, M Hind. Leucocyte Biology, National Heart and Lung Institute, Imperial College London, London, UK

**S99**

EFFECTS OF DIFFERENTIAL TNF RECEPTOR SIGNALLING IN MODULATING NEUTROPHIL-ENDOTHELIAL INTERACTIONS IN THE PULMONARY MICROVASCULATURE

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Neutrophil recruitment into the bronchoalveolar space is central to the pathogenesis of acute respiratory distress syndrome injury (ARDS), and occurs via interaction with the lung microvascular endothelium. Tumour Necrosis Factor (TNF) is a key mediator in these processes, activating endothelial cells and inducing changes in microvascular permeability, as well as priming neutrophils (a pre-requisite for neutrophil-mediated tissue damage) and modulating neutrophil lifespan. TNF signals through two cell surface receptors, TNFR1 and TNFR2 initiating distinct signalling pathways and cellular responses. In a human *in vivo* model of ARDS, selective TNFR1 antagonism attenuated pulmonary inflammation (O’Kane et al, Thorax 2013; 63:A50). Using TNF receptor specific muteins and a novel highly selective TNFR1 antagonist, we investigated the role of differential TNFR signalling on neutrophil-pulmonary microvascular endothelial cell interactions.

TNF-induced alterations in the expression of the neutrophil cell surface molecules CD11b, CD62L, TNFR1 and TNFR2 were all modulated via TNFR1. TNFR1 was also the dominant receptor mediating reactive oxygen species generation by TNF-primed, fMLP-stimulated neutrophils. We further examined the role of TNF receptors in modulating neutrophil apoptosis; whilst engagement of both TNFR1 and 2 was required to induce early neutrophil apoptosis, TNFR1 antagonism reversed TNF-induced late survival to constitutive levels of apoptosis. TNFR1 antagonism of human pulmonary microvascular endothelial monolayers significantly reduced TNF-induced production of IL-1beta, IL-6 and IL-8 (p < 0.05), endothelial permeability and the release of the endothelial injury markers sICAM-1, sVCAM-1 and sE-selectin (p).

Collectively, these results suggest that TNFR1 regulates multiple components of neutrophil-endothelial interactions. Selective TNFR1 antagonism may offer a novel therapeutic approach in ARDS; phase II clinical trials of this therapy are scheduled.

**S100**

PROTEINASE-ACTIVATED RECEPTOR 1 SIGNALLING CONTRIBUTES TO NEUTROPHILIC INFLAMMATION AND ALVEOLAR BARRIER DISRUPTION IN STREPTOCOCCUS PNEUMONIAE PNEUMONIA

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**Introduction**

*Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia (CAP) and is associated with excessive neutrophilic inflammation. The high-affinity thrombin receptor, proteinase-activated receptor (PAR)-1, has been implicated in mediating the interplay between coagulation and inflammation. However, its role during *S. pneumoniae*-induced neutrophilic inflammation and the mechanisms for neutrophil recruitment in this context are poorly understood.