Brighton and Sussex University Hospitals NHS Trust

CIRU Brighton and Sussex Clinical Investigation and Research Unit

NCIN national cancer intelligence network
Using information to improve quality & choice

Simplifying the measurement of co-morbidities and their influence on chemotherapy toxicity

Dr Rajesh Sinha BSc MBBS MRCP, Clinical Research Fellow in Medical Oncology

Brighton and Sussex University Hospitals NHS Trust

Dr Alistair Ring MA BM BCh MRCP MD, Senior Lecturer and Honorary Consultant in Medical Oncology

Introduction

Cytotoxic chemotherapy is used in the treatment of cancer to reduce the risks of disease recurrence following surgery (the adjuvant setting), and to prolong life and improve symptoms in those with metastatic disease (the palliative setting). Chemotherapy is associated with side-effects which include hair loss, lethargy, nausea, mucositis, diarrhoea, organ damage and risks of severe infection. It is difficult to predict which patients are likely to get side-effects, and the presence of co-morbidities and fitness plays a significant role in how cancer patients tolerate treatment. This therefore has an impact in the physicians' choice/decision of chemotherapy usage and regimen for an individual patient. However there is no-one agreed gold standard method of using and measuring co-morbidity and fitness, and how this influences treatment. A recent survey of the NCIN site-specific clinical reference groups suggested that co-morbidities influenced decisions regarding chemotherapy across all tumour sites, and predicting chemotherapy toxicity has been highlighted as an area of critical importance by the National Chemotherapy Advisory Group report in 2009.

Objectives

Primary Aim

To ascertain if the G8 score predicts severe chemotherapy toxicity defined as grade III/IV toxicity (CTCAE version 3.0 criteria), dose reduction, unplanned hospitalization, treatment discontinuation, or death within 30 days of treatment.

Secondary Aims

(i) To ascertain if the VES-13 score ($\leq$ 3 vs. >3) or WHO PS (0, 1 vs. >/=2) predict severe chemotherapy toxicity (defined as above).

(ii) To compare the sensitivity and specificity of G8, VES-13 and WHO PS scores as diagnostic tests in predicting risk of chemotherapy toxicity.

(iii) To compare the co-morbidity index scoring between physician and healthcare assistant by two methods from two sources

(iv) To compare Charlson Co-Morbidity Index Scoring between hospital notes and Hospital Episode Statistics data

Study Design

Prospective cohort study.

Study population

Patients referred for cytotoxic chemotherapy in the Sussex Cancer Network: Brighton and Sussex University Hospital, Worthing and Eastbourne District General Hospitals.

Inclusion criteria

1. Patients aged $\geq$ 18 years.
2. Diagnosed with cancer.
3. Planned to be treated with a new course of cytotoxic chemotherapy, in any treatment setting.
4. Written informed consent.

Exclusion criteria

1. Patients unable to give informed consent.
2. Patients with a life expectancy of less than 8 weeks.
3. Patients due to receive targeted (non-cytotoxic) therapy.
4. Patients who are part way through a chemotherapy course.

Study conduct

From August 2009 to August 2011, we asked all patients aged 18 or over commencing a new course of cytotoxic chemotherapy (in the curative or palliative settings) to enter this study. Recruitment was from the hospitals comprising the Sussex Cancer Network. Patients provided written informed consent, and were asked to complete questionnaires regarding their performance status, fitness

screening test (G8 score) and their functional status (VES-13). Consent for access to hospital notes (HN), primary physician summaries (PPS) and Hospital Episode Statistics (HES) data was also requested. Co-morbidity scoring was undertaken measuring the two scoring indices, the Charlson Co-Morbidity Index (CCI) and ACE-27. Scoring was conducted both by a physician (PHY) and also a healthcare assistant (HCA). The proof of principle that Charlson score can be extracted from HES data has already been provided by the Northern and Yorkshire Cancer Registry and Information Service. They kindly provided the assistance required to extract the scores from HES data supplied by Trusted Data Linkage Service (TDLS) & HES extracts (AHES, MMES) Health & Social Care Information Centre. HN and PPS were coded from the start of the available record to the date of the first course of chemotherapy. HES data were available from 1997 onwards only.

In order to compare the scorers, the hospital notes and primary physician summaries were coded for both scores by both healthcare assistant and physician independently. In order to compare scoring source data, the hospital notes, primary physician summaries and HES data were scored by the physician and the hospital notes and primary physician summaries by the healthcare assistant. In all cases scoring was conducted in a blinded manner and physician scoring from hospital notes was defined as the gold standard. With the introduction of a healthcare assistant being involved in this process, it was hoped that this could be an extended role, at little or no extra cost, as they represent a well-placed, economical pre-existing staff group.

Patients received chemotherapy as part of normal care. Other baseline tumour and demographic data were recorded from the chemotherapy records/patient notes. Data regarding adverse outcomes: toxicity (grade III/IV by CTCAE version 3.0 criteria), dose delays/reductions, death and hospitalization were recorded from the electronic chemotherapy prescribing system, supplemented by the medical records. Severe chemotherapy toxicity was prospectively defined as grade III/IV toxicity (CTCAE version 3.0 criteria), dose reduction, unplanned hospitalization, treatment discontinuation, or death within 30 days of treatment.

In order to analyse the data for comparisons two way contingency tables were constructed and agreement described by Cohen's kappa. It was planned that agreement would be regarded as substantial if 0.61 ≤ kappa ≤ 0.80 and good if kappa > 0.80. Poorer agreement would be defined as poor if kappa ≤ 0.20, fair if 0.21 ≤ kappa ≤ 0.4 and moderate if 0.41 ≤ kappa ≤ 0.60. Analysis of functional status and prediction of chemotherapy toxicity was to be examined by using the Chi-Squared test (or Fisher's Exact Tests where appropriate).

This study was approved by the Brighton East Research Ethics Committee (REC 09/H1107/60) and by Research and Development Departments in participating Trusts

Baseline Demographics

533 patients were invited to take part in the study and 464 (87%) had hospital notes available at the time of analysis, but we could only generate a co-morbidity score in all but six of these hospital notes (therefore total analysed were 458). Primary physician summaries were available for 323 (71%) and HES data available for 320 (70%) and we were able to generate a score in all PPS and HES data provided. Of the 458 co-morbidity scores generated from hospital notes, 402 (88%) had full chemotherapy toxicity recorded. The baseline characteristics of the study population of those whom we scored co-morbidity (n=458) are shown in **Table 1**. Regarding the baseline demographics of age, gender, cancer sites and treatment intent, there was no obvious unexpected finding.

Table 1 - Baseline characteristics of study population (n=458). Data are numbers (percentage) unless stated otherwise

Characteristics	Total (n=458)
Age (years)	
Mean (SD), range	60.89 (SD 11.45), 23-84
< 40	18 (3.9%)
40-49	66 (14.4%)
50-59	95 (20.7%)
60-69	173 (37.8%)
70-79	94 (20.6%)
≥ 80	12 (2.6%)
Gender	
Female	267 (58.3%)
Male	191 (41.7%)
Cancer site	
Breast	128 (27.9%)
Lower GI	80 (17.4%)
Lung	58 (12.7%)
Gynaecological	46 (10.0%)
Urological	31 (6.8%)
Upper GI	27 (5.9%)
Head and Neck	26 (5.7%)
CNS	25 (5.5%)
Haematological	24 (5.2%)
Other	13 (2.8%)

Co-Morbidity Scores + Comparison

Distribution of co-morbidity scores:

The co-morbidity scores ascertained by physician scoring of hospital notes (gold-standard) by the Charlson Co-morbidity index and ACE-27 index are shown in **Figures 1 and 2**. Three hundred and nine (67%) patients had a Charlson score of 0, and 230 (50%) had an ACE-27 score of 0.

Figure 1 - Charlson co-morbidity score (CCI) by Physician from Hospital Notes (n=458)

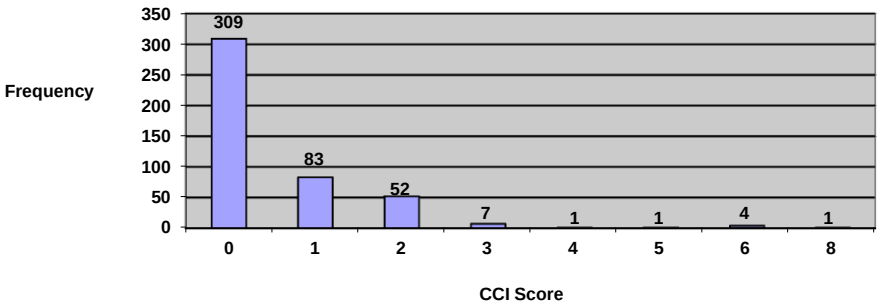
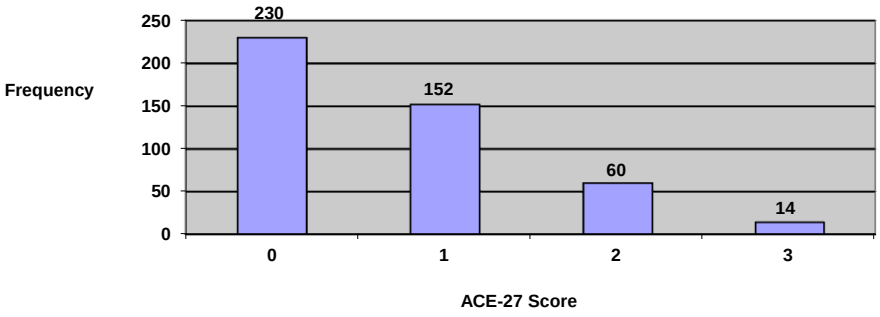


Figure 2 - ACE-27 scores by Physician from Hospital Notes (n=458)

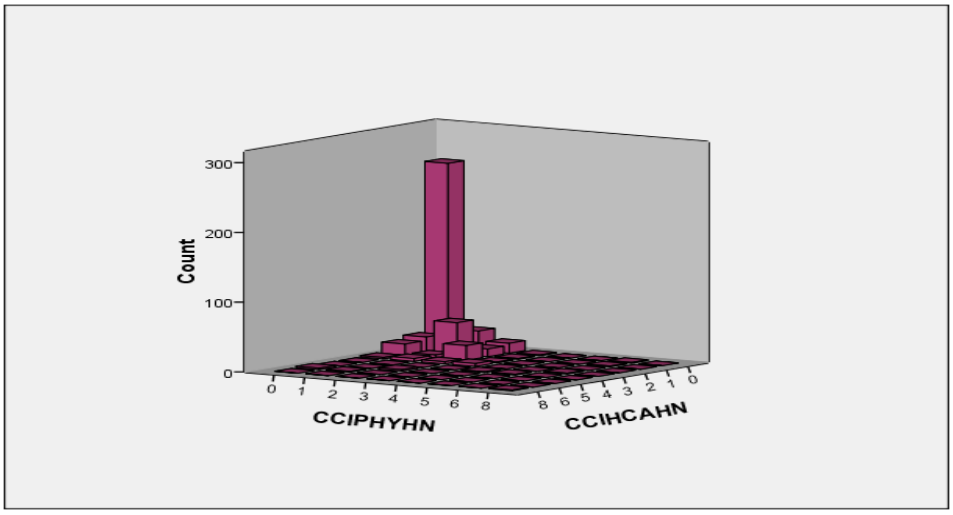


CCI scoring comparison between Physician and Health Care Assistant from Hospital Notes and Primary Physician Summaries

452 sets of hospital notes and 323 Primary Physician Summaries were accessed independently. Kappa score for CCI comparison from Hospital Notes was 0.51 (SE

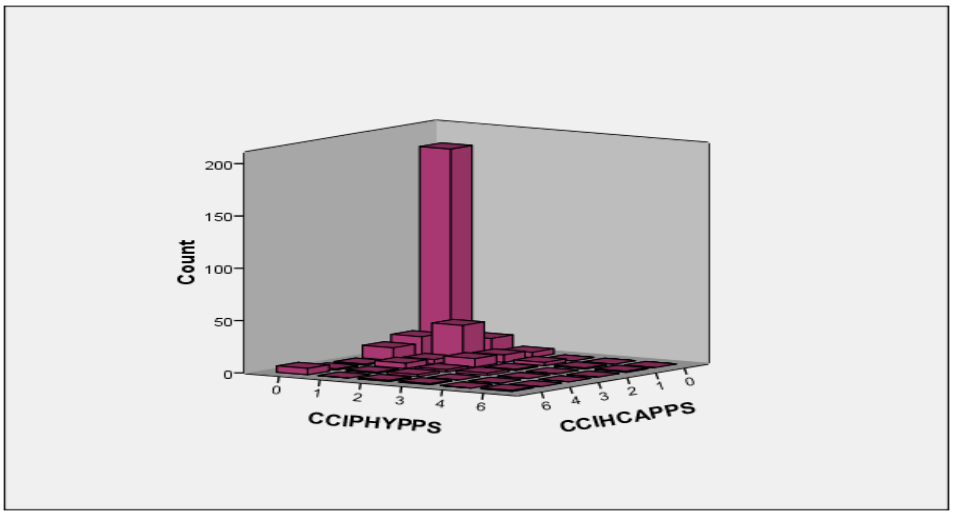
0.19), whilst the Kappa score for CCI comparison from Primary Physician Summaries was 0.42 (SE 0.22). Absolute numbers are displayed in **Figures 3 and 4**.

Figure 3 - CCI comparison scores between PHY and HCA from HN



Kappa 0.51 (SE 0.19)

Figure 4 - CCI comparison scores between PHY and HCA from PPS

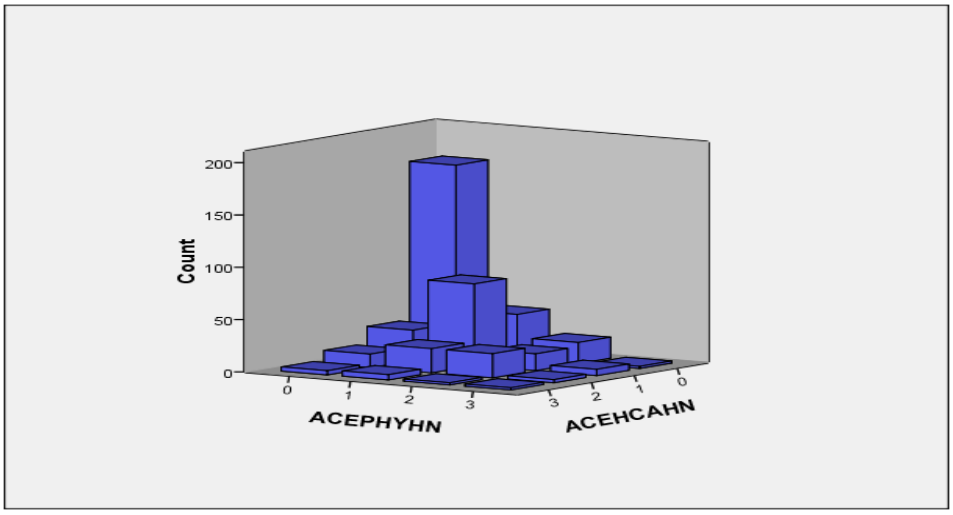


Kappa 0.42 (SE 0.22)

ACE-27 scoring comparison between Physician and Health Care Assistant from Primary Physician Summaries

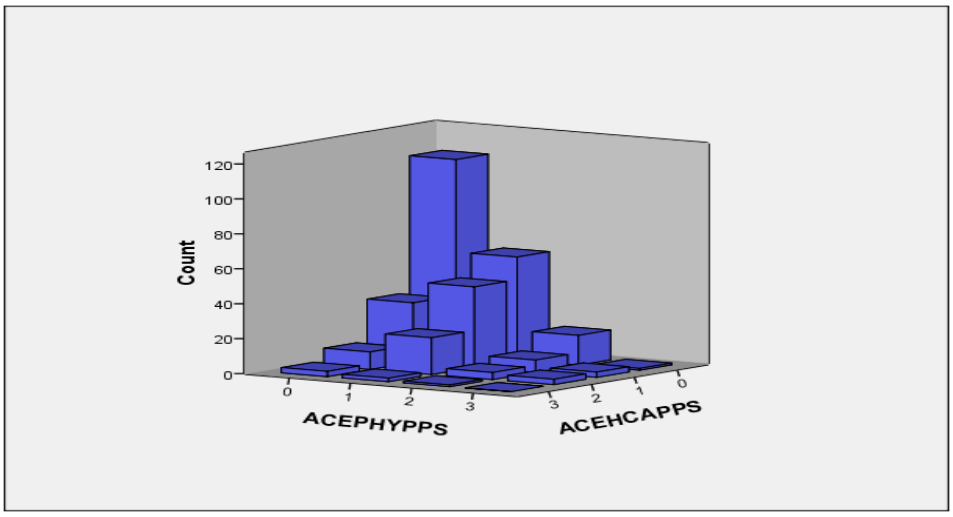
Kappa score for ACE-27 from Hospital Notes was 0.397 (SE 0.034), whilst for ACE-27 from Primary Physician Summaries was 0.153 (SE 0.041). Absolute numbers are displayed in **Figures 5 and 6**.

Figure 5 - ACE comparison scores between PHY and HCA from HN



Kappa 0.397 (SE 0.034)

Figure 6 - ACE comparison scores between PHY and HCA from PPS



Kappa 0.153 (SE 0.041)

Summary of scoring comparison between Physician and Health Care Assistant

The following possible agreements could be summarised **(Table 2)**

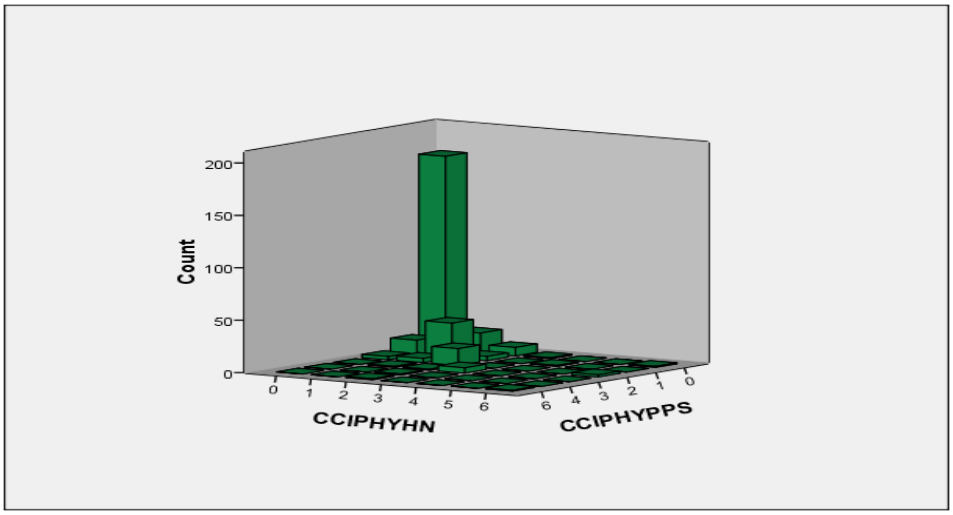
Table 2 - Possible Agreement between scorers

Co-Morbidity	Source	Agreement
CCI	HN	Moderate
	PPS	Moderate to fair
ACE-27	HN	Fair to moderate
	PPS	Poor

CCI/ACE-27 scoring comparison between Hospital Notes and Primary Physician Summaries by Physician

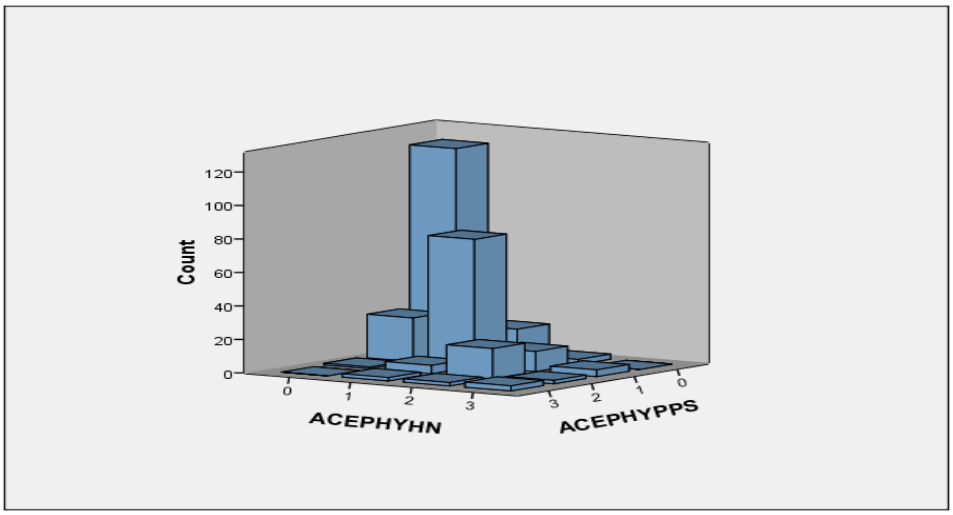
452 sets of hospital notes and 323 Primary Physician Summaries were accessed independently. Kappa score for CCI comparison from Hospital Notes and Primary Physician Summaries by physician was 0.6 (SE 0.22). For ACE-27 comparison from Hospital Notes and Primary Physician Summaries by physician, the Kappa score was 0.57 (SE 0.04). For absolute numbers, refer to **Figures 7 and 8 respectively**.

Figure 7 - CCI comparison scores between HN and PPS by PHY



Kappa 0.6 (SE 0.22)

Figure 8 - CCI comparison scores between HN and PPS by PHY

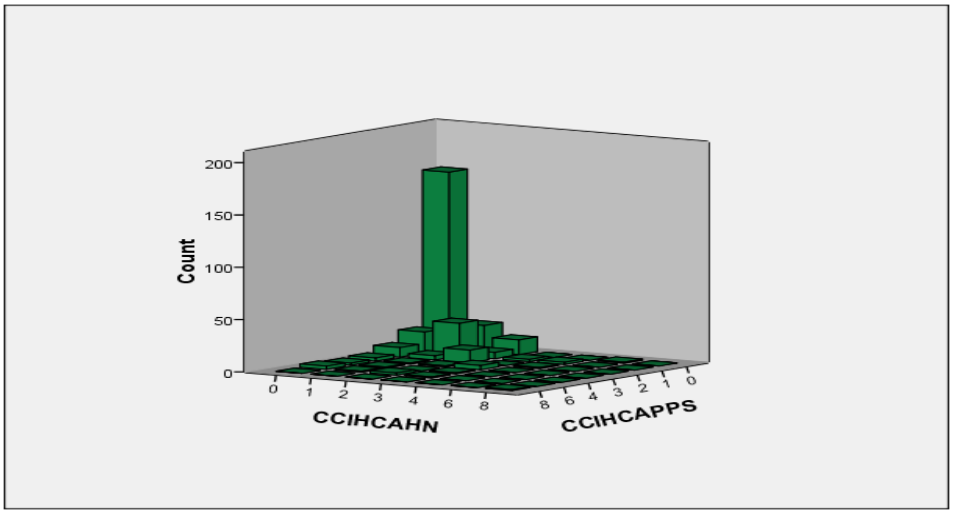


Kappa 0.57 (SE 0.04)

CCI/ACE-27 scoring comparison between Hospital Notes and Primary Physician Summaries by Health Care Assistant

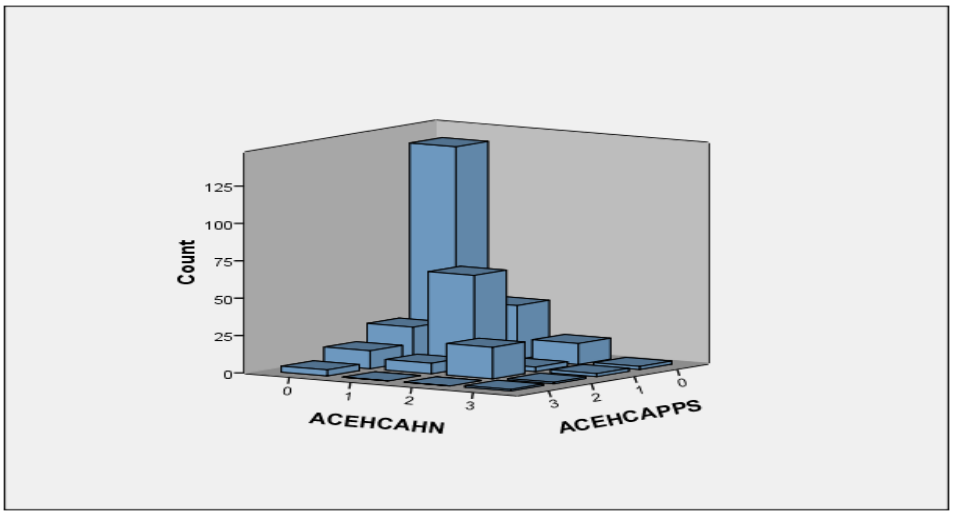
Kappa score for CCI comparison from Hospital Notes and Primary Physician Summaries by health care assistant was 0.4 (SE 0.24). For ACE-27 comparison from Hospital Notes and Primary Physician Summaries by health care assistant, the Kappa score was 0.45 (SE 0.04). For absolute numbers, refer to **Figures 9 and 10 respectively**.

Figure 9 - CCI comparison scores between HN and PPS by HCA



Kappa 0.4 (SE 0.24)

Figure 10 - CCI comparison scores between HN and PPS by HCA



Kappa 0.45 (SE 0.04)

Summary of scoring comparison between sources by scorers

The following possible agreements could be concluded **(Table 3)**

Table 3 - Possible Agreement between scorers

Co-Morbidity	Scorer	Agreement
CCI	PHY	Moderate to substantial
	HCA	Fair to moderate
ACE-27	PHY	Moderate to substantial
	HCA	Moderate

Co-Morbidity Scoring between HES Data and CCI Scoring

Regarding the HES data, 320 patients' data were collected and CCI scored. The proof of principle that Charlson score can be extracted from HES data has already been provided by the Northern and Yorkshire Cancer Registry and Information Service. They kindly provided the assistance required to extract the scores from HES data supplied by Trusted Data Linkage Service (TDLS) & HES extracts (AHES, MMES) Health

& Social Care Information Centre. The Kappa score was 0.56, SE 0.05. The agreement between the expected gold standard CCI HN PHY score to CCI PHY HES score could be potentially concluded as moderate, favouring substantial.

Chemotherapy toxicity and co-morbidity score

Regarding co-morbidity scores and prediction of severe chemotherapy toxicity, there were 402 full sets of concordant data of co-morbidity score and presence/absence of severe chemotherapy toxicity. Poor co-morbidity score was defined as CCI ≥2 and ACE-27 ≥2. Severe chemotherapy toxicity was experienced by 250 (55%) of patients. Of patients with a CCI ≥2 score, 61% (34/55) experienced severe chemotherapy toxicity compared with 62% (216/347) of those with a CCI<2 ($\chi 2$ =0.19, p =0.891). Of patients with an ACE-27 score of ≥2, 62% (41/66) experienced severe chemotherapy toxicity compared with 62% (209/336) of those with an ACE-27 score <2 ($\chi 2$ =0.30, p =0.863). Poor co-morbidity score did not predict severe chemotherapy toxicity **(Table 4)**.

Table 4 - Cross-tabulation co-morbidity score (0-1 vs. ≥2) and severe chemotherapy toxicity

	Severe Toxicity Present	**Severe Toxicity Absent**	**Total**
CCI			
0 OR 1	216	131	347
≥2	34	21	55
TOTAL	250	152	402
ACE-27			
0 OR 1	209	127	336
≥2	41	25	66
TOTAL	250	152	402

A sub-set analysis of the over-65 age group and their co-morbidity scores and prediction of chemotherapy toxicity again found no significant correlation found both with CCI (Score 0-1 vs. ≥2, χ^2=0.164, p=0.685) and ACE-27 (Score 0-1 vs. ≥2, χ^2 =1.090, p=0.296).

Functional Status + Prediction of Chemotherapy Toxicity

G8 score and Chemotherapy toxicity

The G8 score is a measure of functional status, nutrition and symptomology. G8 scores of </= 14 has been shown to be predictive of failing a comprehensive geriatric assessment. The G8 score was recorded in 448 patients. Table 1 reveals the absolute numbers and percentages of the G8 score versus chemotherapy toxicity. Regarding any significance, the Chi Squared score was X^2 =2.198 and p=0.138, therefore not felt to be significant, or predictive **(Table 5)**.

Table 5 - G8 scores and chemotherapy toxicity

	Toxicity	Present {%}	Absent {%}	Total
G8 score	0-14	113 {66%}	56 {34%}	171
	>14	167 {60%}	110 {40%}	277
		282	166	448

VES-13 and Chemotherapy toxicity

This Questionnaire measures functional capacity. The 13-item covers age, self-rated health, limitations in physical function and functional disabilities. A score of more than 3 is predictive of death and functional decline in older patients. Table 2 represents the absolute numbers and percentages of the VES-13 scores versus chemotherapy toxicity. The Chi-Squared score was X^2 = 6.799 and p=0.009 Therefore, this was felt to be significant **(Table 6)**.

Table 6 - VES-13 scores and chemotherapy toxicity

	Toxicity	Present {%}	Absent {%}	Total
VES-13	≥3	194 {59%}	133 {42%}	327
	<3	88 {73%}	33 {37%}	121
		282	166	448

Performance Status and Chemotherapy toxicity

Performance Status is a universally accepted method of assessing fitness. It is still considered the gold standard method and its practice is widespread. Table 3 reveals the absolute numbers and percentages of the Performance Status scores versus chemotherapy toxicity. The Chi-Squared score was X^2=2.681 and p=0.102. Therefore this was felt not to be significant **(Table7).**

Table 7 - Performance Status scores and chemotherapy toxicity

	Toxicity	Present {%}	Absent {%}	Total
PS	≥2	81 {69%}	36 {31%}	117
	0-1	201 {61%}	130 {39%)	331
		282	166	448

Conclusions

Undertaking this study, with over 500 patients was a substantial task, carried out by a number of researchers over a two year period. On to the issue of co-morbidity and what role this can play in fitness assessment and prediction of chemotherapy toxicity, but there is no one gold standard, widely accepted tool, and more importantly, given the time it takes to score morbidity, no one single accepted source, nor accepted coder. This study tried to answer a number of these points raised. Given the previous experience of researchers in the Sussex Cancer Network of using functional status to assess patients in previous and current running studies, it was prudent to gain further data on a significant cohort of patients. Functional status to assess fitness has long been suggested to supersede performance status as a more objective way of predicting how well a patient may tolerate treatment. This is especially important in the older patient.

Co-Morbidity

The ageing of the cancer population brings with it a number of challenges. Amongst these is the need to develop robust measures of health and fitness to guide clinical decision-making. One aspect of this is the introduction of objective measures of co-morbidities into clinical and research practice. This study explores ways to simplify co-morbidity scoring, attempting to circumvent the use of physicians coding sets of hospital notes. As a secondary objective the study explores whether co-morbidity scores predict chemotherapy toxicity.

In this cohort of patients receiving chemotherapy the co-morbidity scores were skewed. This was most striking for the CCI, where 85% of patients had a score of 0 or 1.

One might have anticipated the particular skewing in this cohort, given that the majority of patients deemed fit enough for (and therefore receiving) chemotherapy are likely to have a low burden of co-morbidities. This may limit the ability of the Charlson index (and to a lesser extent ACE-27) to discriminate between different groups, and their likelihood of toxicity in this context.

Scoring co-morbidity is challenging with problems of source availability and accuracy and time taken to carry out the scoring. This project therefore sought to pilot more efficient ways to score co-morbidities using non-physician staff and different sources of co-morbidity data to code. Regarding the coder, it was felt that a Health Care Assistant could provide a more economical and time saving process. However in this study there was little agreement between the health care assistant and the physician, with the possible exception of when scoring was performed of CCI from the hospital notes (Kappa 0.51). Regarding source data, hospital notes are considered the gold standard source, but accessing these and reviewing them is time-consuming. Primary Physician summaries tend to be 1-2 pages long, and may offer a briefer summary which is quicker and easier to code, in addition to recording some conditions which have not come to the attention of secondary care. There was reasonable agreement between hospital notes and primary physician summaries (when scored by a physician, Kappa 0.6 for CCI), meaning that these summaries may prove to be a suitable source for co-morbidity ascertainment. Hospital Episode Statistics also appeared to be a reasonable source of data for scoring (Kappa 0.56 for physician scoring CCI). This process was time-consuming, but under some circumstances HES data may be the only source of co-morbidity data available.

This project provides some evidence that it may not be necessary to use the gold-standard data approach of a physician-coding hospital notes to record co-morbidity data. Coding from Primary Physician Summaries accompanying many two-week wait cancer referrals or the use of a health care assistant may be reasonable. There was also reasonable agreement with HES data. Whilst time-consuming the latter development is important, as it would facilitate remote attribution of co-morbidities as part of cancer registry studies or clinical trial datasets.

Functional Status and prediction of chemotherapy toxicity

The above results looking at G8, VES-13 and PS scores and how they were possible predictors of chemotherapy toxicity were thought provoking. It must be mentioned that self assessment of functional status by patients is perceived to be the ideal method of obtaining the scores, as especially oncologists tend to use performance

status as the gold standard, and this score tends to be generated immediately or within a couple of minutes following a oncologist-patient consultation. However an interpretation of what a patient feels they can do for themselves varies with age and social circumstances.

It appears though with the results that a VES-13 score appeared to be a promising predictor of chemotherapy toxicity, whilst G8 score and PS were not so promising. However the limitations of scoring especially in the G8 score were resultant of some of its components including nutritional assessment and psychological problems. There were more VES-13 scores generated than G8 scores. Performance Status as much as being a subjective method of scoring fitness by a physician, has similar problems when a patient tries to fill out a form asking these questions. Regarding the scoring of chemotherapy toxicity, the data was mainly derived from the electronic chemotherapy database and patients' notes, but all the treatment related toxicity may have not been recorded.

Overall, this study suggests that scoring co-morbidity from Primary Physician Summaries appears to be a reasonable and less time-consuming process, but with a suggestion that a trained medical physician is still recommended, but poor co-morbidity score did not appear to predict severe chemotherapy toxicity. Regarding functional status, VES-13 appears to be a promising predictor of chemotherapy toxicity, rather than the rather subjective widely accepted and used Performance Status.