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Abstract

Imatinib therapy has improved outcomes in advanced GISTs. Current guidelines suggest monitoring with CT scanning every 12 weeks. There are no validated biomarkers to assist disease evaluation. We identified 50 patients treated with imatinib for GIST in a single tertiary centre. We assessed the prognostic value of d-dimers by Cox regression, and the utility as a biomarker for radiological progression (rPD) using receiver-operator curve (ROC) analysis. In asymptomatic patients with d-dimer levels <1000 and falling levels, the negative predictive value for rPD was 92%. D-dimers may reduce the burden of CT scanning in a proportion of patients in this setting.

Background

The use of imatinib, a molecularly targeted agent against the tyrosine kinase receptor, has led to improved tumour control and a survival advantage in patients with locally advanced and metastatic GISTs¹⁻³. Benefits have also been seen in second line treatment with sunitinib, following progression with, or intolerance of, imatinib. With the availability of second line therapies, disease monitoring whilst on imatinib is important to identify cancer progression in a timely manner. CT scanning is the imaging modality recommended by established guidelines for routine monitoring. Specific guidelines suggest that CT scans to assess response should be performed up to 3 monthly, for an indefinite time period⁴⁻⁷. Such frequent scanning aims to identify progression early, but as patients may remain progression-free for a number of years, it comes with a burden of cost, radiation exposure and consequences for the patient experience. In contrast to other cancers, there are currently no non-radiological biomarkers to aid in the response assessment of GIST.

D-dimers are commonly used in the diagnostic assessment algorithm for the exclusion of venous thrombosis due to their high negative predictive value (NPV) for this condition⁸. They are also raised in other conditions and therefore have a poor positive predictive value (PPV). As a result D-dimers are useful for ruling-out, rather than ruling-in, thrombosis. D-dimers are frequently raised in the presence of active cancer and are associated with poor survival outcomes⁹. For this reason it seems possible that they can help to rule out active or progressing cancer.

D-dimers have been measured approximately 3-monthly in patients with advanced GIST in our centre over the last 10 years. We investigated whether D-dimers can predict disease progression in patient with GIST treated with palliative imatinib therapy. The objective was to determine if D-dimers can offer sufficient negative predictive value for radiological progression to reduce the frequency of CT scanning.

Patients & Methods

Patients were eligible for inclusion in the study if they had been treated with imatinib as palliative treatment for histologically confirmed incurable GIST between 1st January 2000 and 1st January 2010. The study was limited to St. James's University Hospital in Leeds, UK which is a single large tertiary referral centre. Patients were identified retrospectively using a systematic search of an electronic patient records database (Patient Pathway Manager - PPM¹⁰). Patients were excluded if their care was transferred to another centre or if they were treated elsewhere under advice from St. James's University Hospital. Baseline clinical

1
2 characteristics were recorded and were pre-defined as age at presentation, sex, performance status, site of
3 primary tumour, presence of metastases at presentation, neutrophil count and baseline D-dimer level.
4 Routine follow-up consisted of clinic attendance with clinical assessment at 3-monthly intervals with a D-
5 dimer blood test before each visit and a CT scan at 3 monthly intervals (alternate clinic visits). The D-dimers
6 were analysed using the HemosIL D-dimer Kit by Beckman Coulter.
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11 ***Endpoint definitions***

12 Response assessment was measured by CT scan reported to standard criteria (the adopted criterion in the
13 department was changed from RECIST to Choi in 2004). Clinical benefit was defined as complete response,
14 partial response or stable disease. Day zero was taken as the date of the commencement of imatinib. Survival
15 endpoints were progression free survival (PFS) and overall survival (OS). PFS was defined as time to first
16 radiological evidence of progression or death from any cause, with patients censored at last follow-up. OS
17 was defined as time to death from any cause, with patients censored at last follow-up.
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25 The D-dimer measurement associated with each scan was that taken closest to each CT scan date. Any D-
26 dimer measurement that was taken more than 30 days either side of the CT scan was excluded.
27 Assessment of the ability of D-dimers to exclude radiological progression took two separate approaches.
28 The first ('D-dimer level') took the reported value at the time of the scan. The second approach ('D-dimer
29 trend') took the difference in the level between two sequential scans, irrespective of the time interval
30 between measurements.
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37 ***Statistical Analysis***

38 The Kaplan-Meier method was used for survival analysis. A log-rank test was used to test for significant
39 prognostic ability of baseline D-dimer levels. Adjustment for baseline clinical characteristics previously
40 identified as prognostic in advanced GIST was undertaken using the Cox proportional hazards model¹¹⁻¹³.
41 Genetic mutation analysis was not conducted in patients diagnosed early in the series therefore this was not
42 considered. Highly correlated variables were excluded if they demonstrated an absolute correlation coefficient
43 > 0.4 using a Spearman rank correlation (no variables required exclusion). D-dimer level was also included in
44 a Cox-proportional hazards model as a time-dependent co-variate¹⁴. The D-dimer level at the time of each CT
45 scan was compared to the response assessment (progressive disease vs clinical benefit) with medians
46 compared using the Wilcoxon rank sum test. The mean change (trend) was compared using a Welch's t-test.
47 A two-sided p-value of less than 0.05, in all tests, was considered statistically significant. Receiver operating
48 characteristic (ROC) analysis was conducted using established methods¹⁵. The
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2 predictive ability of both the absolute D-dimer level and the trend (change over time) was assessed. R
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4 version 2.11.1 was used for the statistical analysis¹⁶.

7 **Results**

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9 A total of 50 patients were included in the study. Patient characteristics are summarized in Table 1. There
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11 were no patients diagnosed with venous thromboembolism during the study period.

12
13 The median follow-up at the time of analysis (January 2012) was 3.7 years overall or 4.7 years in patients
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15 who remain alive and progression-free. 41 patients (82%) experienced events meeting the definition of PFS.
16
17 The median PFS was 2.2 years. 29 patients (58%) had died and the median OS was 4.9 years.

19 **D-dimers as a prognostic indicator**

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21 A baseline D-dimer measurement of >1000 ng/ml was prognostic for PFS ($p = 0.00002$, unadjusted hazard
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23 ratio 5.55) and OS ($p = 0.000007$, unadjusted hazard ratio 7.9) (Figure 1). This remained significant when
24
25 adjusted for all other baseline factors in bivariate and multivariable analysis. D-dimers were more strongly
26
27 prognostic for PFS and OS when analysed as a continuous time-dependent covariate.

29 **D-dimers as a predictor of disease activity**

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31 In total, across all patients there were 460 observation points which included a CT scan, D-dimer
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33 measurement and clinical assessment. The median D-dimer level when there was no radiological evidence
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35 of progression was 411 ng/ml (IQR 233 – 691) compared to a median level in patients with radiological
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37 evidence of progression of 609 ng/ml (IQR 342 – 1770) ($p = <0.0001$). The median level when there was
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39 radiological or symptomatic evidence for progression was 1238 ng/ml (IQR 591 – 2528) (Figure 2a).

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41 Looking at the change in D-dimer level compared with that measured at the time of the previous scan
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43 (trend), the median change prior to a scan with no evidence of radiological progression was 0 ng/ml (IQR -65
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45 – 67). Patients with radiological evidence of progression had a median change of 80 ng/ml (IQR 0 – 339) (p
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47 <0.0001). The median level of change when there was both radiological and symptomatic evidence of
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49 progression was 189 ng/ml (IQR 0 – 892) (Figure 2b).

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51 ROC curves are presented in Figure 3 for both D-dimer levels, and change in D-dimer levels, demonstrating
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53 the sensitivity and specificity as a biomarker for radiological progression. The area under the ROC curve
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55 (AUC) was 0.64 and 0.65 respectively.

57 **D-dimers as a surrogate marker to exclude radiological progression**

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59 The odds for radiological progression, given different D-dimer levels, change in D-dimer levels prior to a
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scan, and the presence or absence of clinical symptoms are presented in Figure 4. Falling D-dimers are
URL: <http://mc.manuscriptcentral.com/lcnv> E-mail: glyman@fhcrc.org

1
2 associated with odds for radiological progression of 0.28 (95% CI 0.15 – 0.48, $p < 0.001$), are seen in 39% of
3 observations and have a negative predictive value (NPV) for excluding radiological progression of 0.91. The
4 ability of D-dimers to exclude radiological progression is improved by considering patients with falling D-
5 dimers and a level less than or equal to 900 ng/ml. In this case the odds for radiological progression is 0.26
6 (95% CI 0.13 – 0.47, $p < 0.001$) with a NPV of 0.92 in 35% of observations. This is improved further by also
7 considering the absence of clinical symptoms of progression which, when combined with falling D-dimers
8 below the level of 900 ng/ml gives an odds for progression of 0.23 (95% CI 0.11 – 0.43, $p < 0.001$) and a NPV
9 of 0.93, seen in 33% of observations.
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17 **Discussion**

18 Imatinib has greatly improved outcomes in advanced GIST, and these have been further improved with
19 second line therapy using sunitinib. With further therapeutic options and the potential for patients to be
20 monitored on treatment for many months or years, optimal monitoring strategies are vital. Current strategies
21 are formalized by a number of clinical guidelines including those by the European Society for Medical
22 Oncology, US National Comprehensive Cancer Network, and the UK National Institute for Health and
23 Clinical Excellence⁴⁻⁶. For patients on active palliative systemic therapy, monitoring is recommended every 3
24 months using CT scanning. There is little empirical evidence to support this recommendation and such
25 frequent scanning, often over many months or years, places an emotional burden on patients, potentially
26 unnecessary radiation exposure and a financial burden on health service providers.
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37 The results presented here suggest that D-dimer monitoring offers useful information about progression
38 status. We suggest that a combination of three criteria can be considered reassuring of non-progression: i)
39 no clinical evidence of progression, ii) a fall in the D-dimer level since the previous measurement and, iii) a
40 D-dimer level less than 900 ng/ml. The NPV for progression in patients meeting all these criteria is 0.93. This
41 suggests that CT scanning can safely be foregone in patients meeting these criteria. The benefits of
42 adopting D-dimer-directed CT scanning would be to reduce the burden of scans by approximately a third.
43 The negative consequences would be to introduce a delay to diagnosis in around 7% of true progression
44 events. This delay would be incurred until such a time as either the D-dimer level stabilized or rose, or the
45 patient developed symptoms of progression.
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54 Our conclusions make the assumption that our gold-standard test, the CT scan, is a perfect indicator of
55 progression status. However, radiological evaluation is not straight forward for GIST and the interpretation of
56 CT findings can vary between tumours depending upon their size, stage and aggressiveness. Treatment
57 with imatinib can typically take up to 1 year to fulfil RECIST response criteria and it has been demonstrated
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2 that response assessed by RECIST does not correlate well with time to progression^{17,18}. The Choi criteria
3 may improve on RECIST for assessment of response by also taking into account tumour density but,
4 regardless of criteria used, CT scans may not always detect progression. Tumours may enlarge in the
5 context of a response, and progression may only be evident by the development of nodules within an
6 existing tumour. FDG-PET may offer improved test performance for the detection of progression, but its use
7 for serial monitoring is limited by accessibility and cost¹⁸⁻²⁰. We found no data reporting the sensitivity and
8 specificity of imaging modalities for the detection of progression. For these reasons, our reported NPV for
9 D-dimers needs to be interpreted in relation to CT progression detection rather than more meaningful
10 patient outcomes.

11
12 There are currently no validated biomarkers to aid in response assessment or detection of progression in
13 GIST. There are a number of other precedents supporting the use of tumour markers to provide information
14 about progression status. This is perhaps most notable in the case of germ cell tumours, which secrete
15 β -HCG or α -fetoprotein, where tumour markers correlate very strongly with progression and may frequently
16 pre-date radiological detectability; monitoring is a core component of follow-up guidelines²¹. The marker CA-
17 125 is highly correlated with progression status in ovarian cancer²² and CEA is used to monitor the treatment
18 of colorectal cancer.

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20 The activation of the coagulation system is associated with the immune response that accompanies active
21 malignancy. D-dimer is a fibrin degradation product present in the blood when following the activation of the
22 coagulation cascade. There is therefore a mechanistic theory that supports D-dimers as a biomarker for
23 cancer activity. In a number of published studies, D-dimers have been shown to be related to cancer, with
24 high levels associated with the presence of malignancy, higher levels seen in metastatic compared with
25 earlier stage disease and raised in those with active cancer compared to patients in remission²³⁻²⁵. D-dimer
26 levels and changes have demonstrated a relationship with progression status in other studies in lung cancer
27 and breast cancer^{26,27}. As well as being predictive for progression, our data suggests that a high baseline D-
28 dimer is also a prognostic marker for overall survival and progression-free survival. High D-dimer levels at
29 baseline are a poor prognostic sign in several cancers and predictive of lymph node metastases in breast,
30 colorectal and oesophageal cancers^{25,27-36}. Interestingly, in one study, D-dimers were more prognostic for
31 survival than CEA in colorectal cancer patients³⁷. We therefore suggest that D-dimers could usefully be
32 incorporated into future baseline staging information and considered in the formulation of future prognostic
33 algorithms.

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2 The methods for testing and validating tumour markers for use as a monitoring test are under-developed and
3 standards have not yet been formalised³⁸. It seems reasonable to believe that the rate of change over time
4 rather than the absolute level is likely to more accurately reflect cancer activity. It is therefore disappointing
5 that many tumour markers are interpreted on the basis of an absolute value in relation to normal ranges²².
6 This may in part explain the failure of tumour marker monitoring to impact on clinical outcomes in
7 randomised controlled trials³⁹. The methods used in our analysis of D-dimers for GIST demonstrate how
8 decision criteria can maximise the performance of the monitoring test, by combining the absolute level, the
9 rate of change and clinical assessment.
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11 The limitations of this study are that it is a single centre study relying on retrospective data collection. The
12 criteria for interpreting CT tumour status also changed during the 10 years over which our data were
13 collected and this may have led to some inconsistency in reporting and identification of progression dates.
14 Our data also reflects real-world practice rather than being driven by a research protocol. This has some
15 advantages in generalisability to clinical practice, but the findings may have been compromised by factors
16 such as the variability in D-dimer and CT monitoring frequency and non-standard interpretation of findings.
17 Clinical management also evolved during our study as new therapeutic options were introduced such as c-kit
18 directed therapy and second line treatments.
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20 The next steps in the development of D-dimers as a monitoring test would be to repeat the analysis in a
21 separate independent dataset. Following this it may be appropriate to study the effect of D-dimer monitoring
22 on clinical outcomes in the setting of a randomised controlled trial. We would, however, suggest that D-
23 dimers may be usefully adopted to reduce the burden of frequent CT scanning in patients who have
24 experienced a symptomatic and radiological benefit from imatinib and who remain clinically stable.
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Table 1. Patient characteristics at commencement of imatinib.

Characteristic	No of Patients (%)
Total no of patients	50
Sex	
Male	22 (44)
Female	28 (56)
Age	
<=55	10 (20)
56 - 65	14 (28)
66 - 75	17 (34)
>75	9 (18)
Received surgery	28 (56)
Metastases on presentation	38 (76)
Neutrophils >ULL on Presentation	11 (22)
Stomach as Primary	21 (42)
Performance status	
0	26 (52)
1	17 (34)
2	6 (12)
3	1 (2)

ULL = Upper Limit of Normal

* Clinical benefit = radiological response or stable disease.

Figure legend

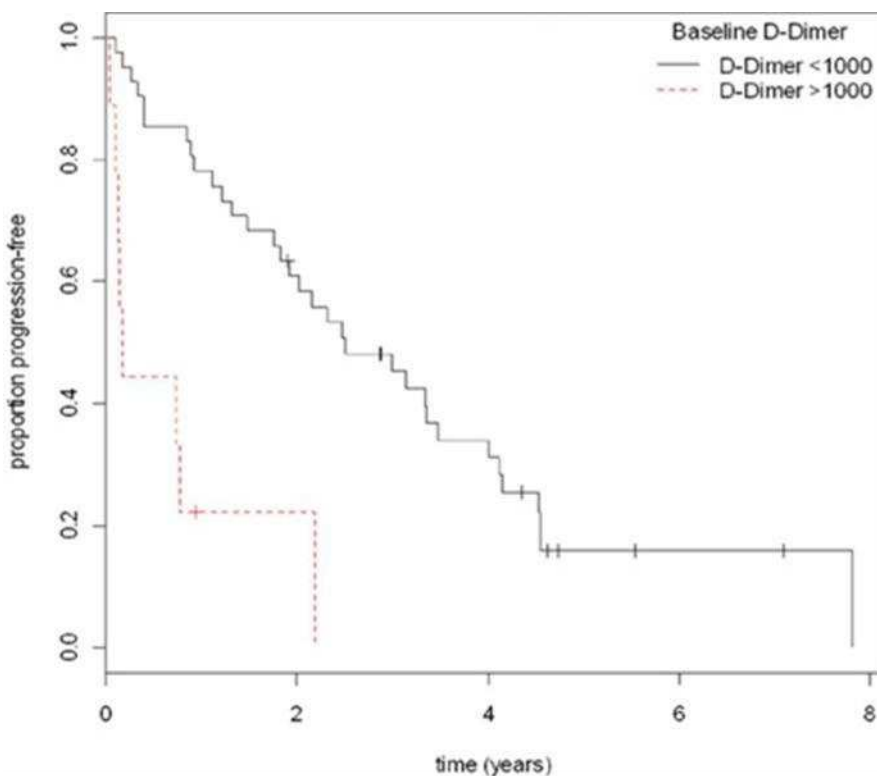
Figure 1a. Kaplan-Meier plot of progression-free survival by baseline D-dimer level. Figure 1b. Kaplan-Meier plot of overall survival by baseline D-dimer level.

Figure 2. Boxplots presenting the median, interquartile range and range given symptomatic and/or radiological progression (rPD) for (a) D-dimer levels and (b) change in D-dimers from previous scan.

Figure 3. Receiver operating curve (ROC) plots for (a) the D-dimer level at the time of CT scan [Area under the curve = 0.64] and (b) the change in D-dimers compared with the measurement at the time of the previous CT scan [Area under the curve = 0.65].

Figure 4. (a) Odds ratios for radiological progression given a D-dimer level above various cut-offs and (b) odds ratios for progression given different combinations of the actual level of D-dimers and change in D-dimers over time and the presence of clinical evidence of symptomatic progression (each odds ratio is derived from a separate logistic model).

Figure 1a



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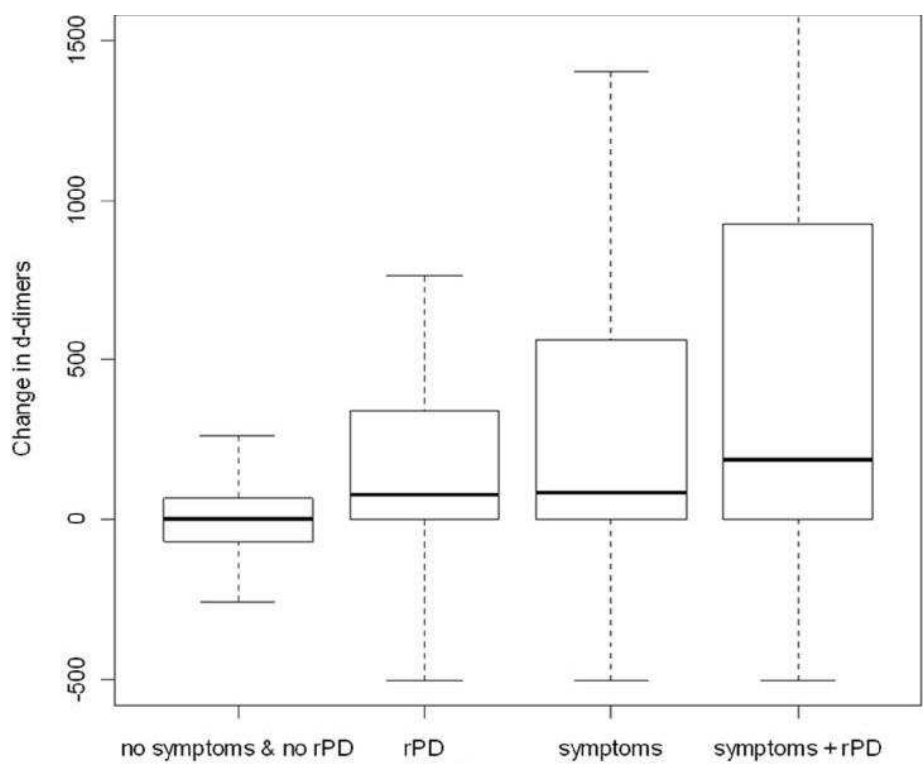


Figure 2b

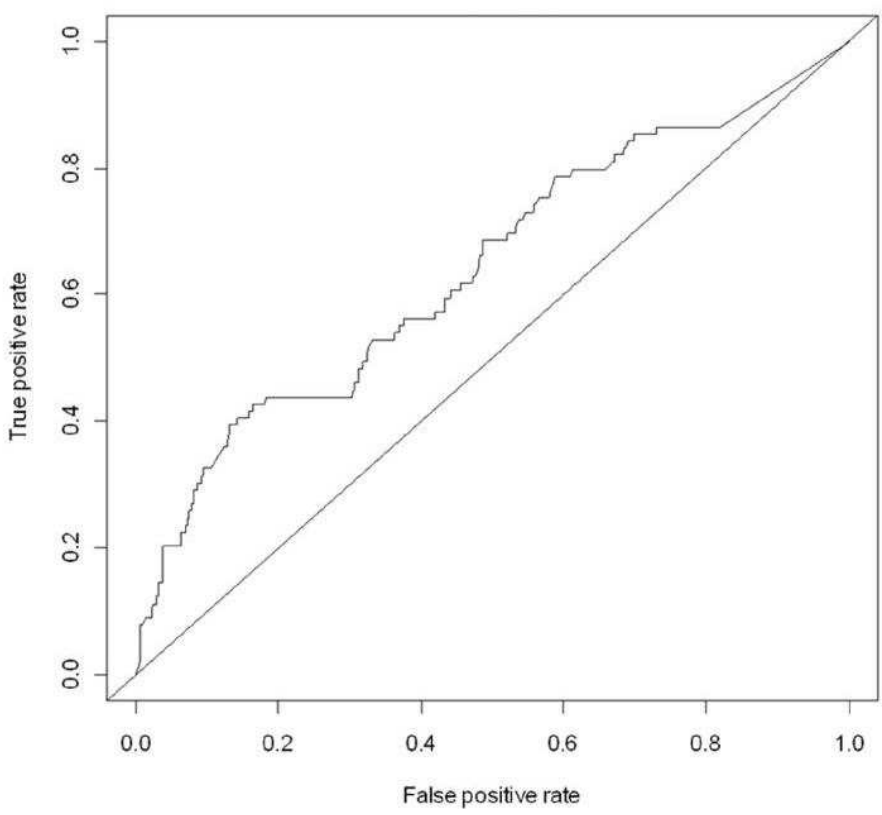


Figure 3a

URL: <http://mc.manuscriptcentral.com/lcnv> E-mail: glyman@fhcrc.org

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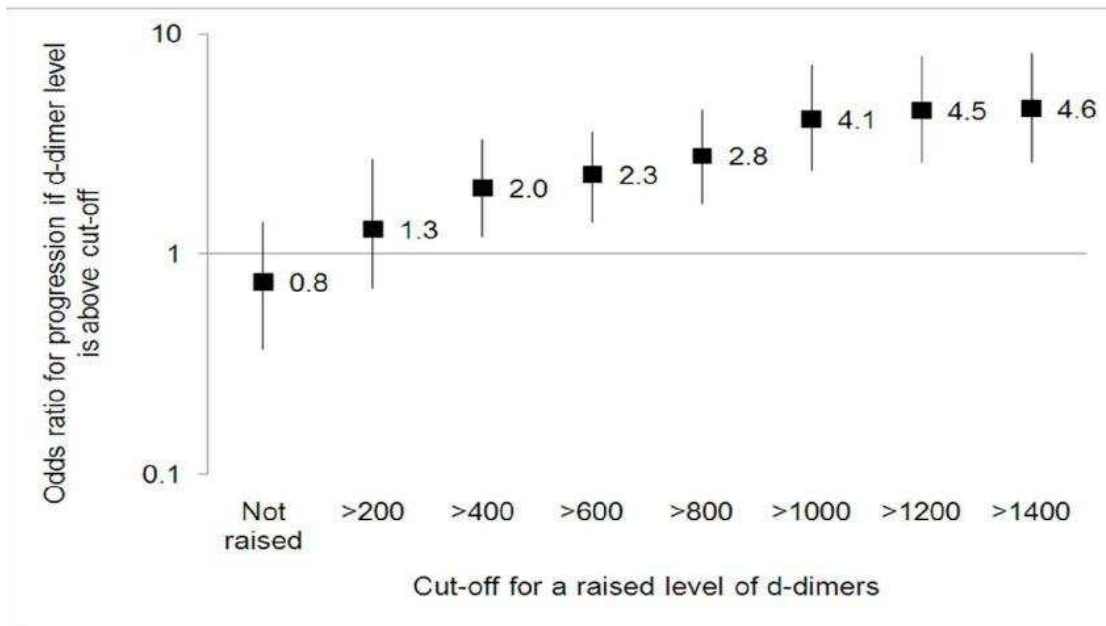
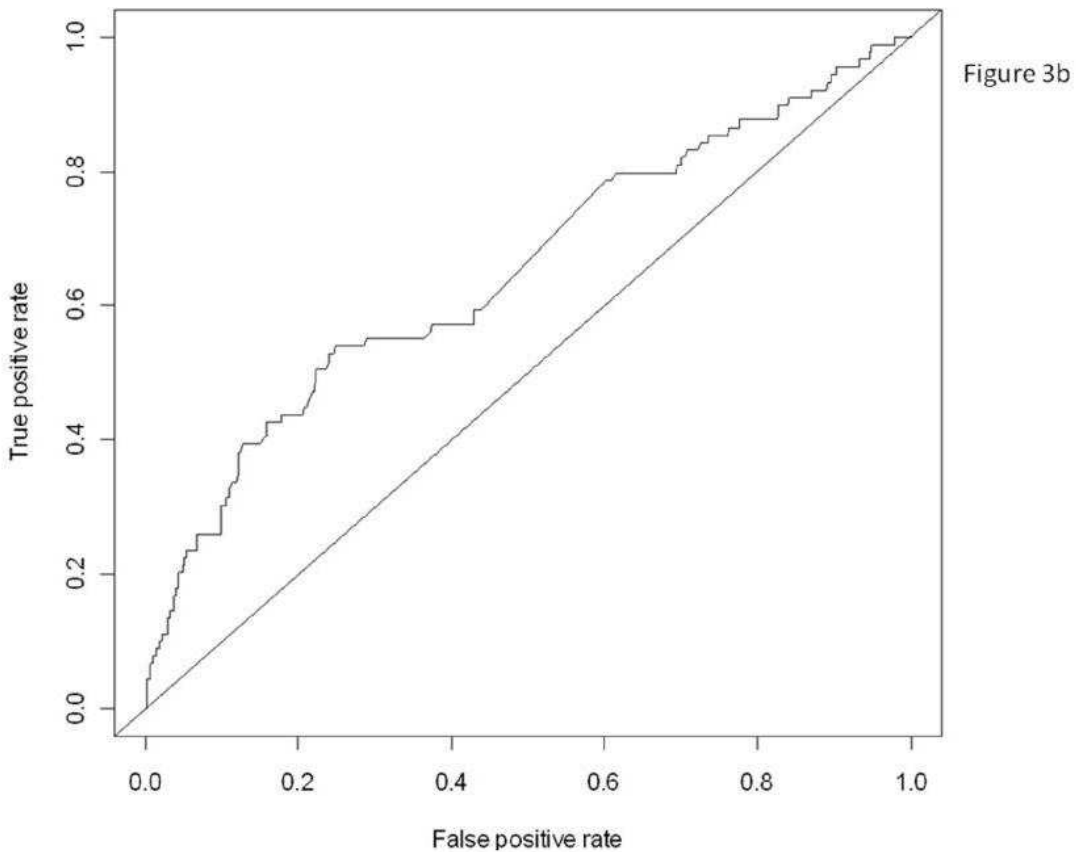


Figure 4a

Cancer Investigation

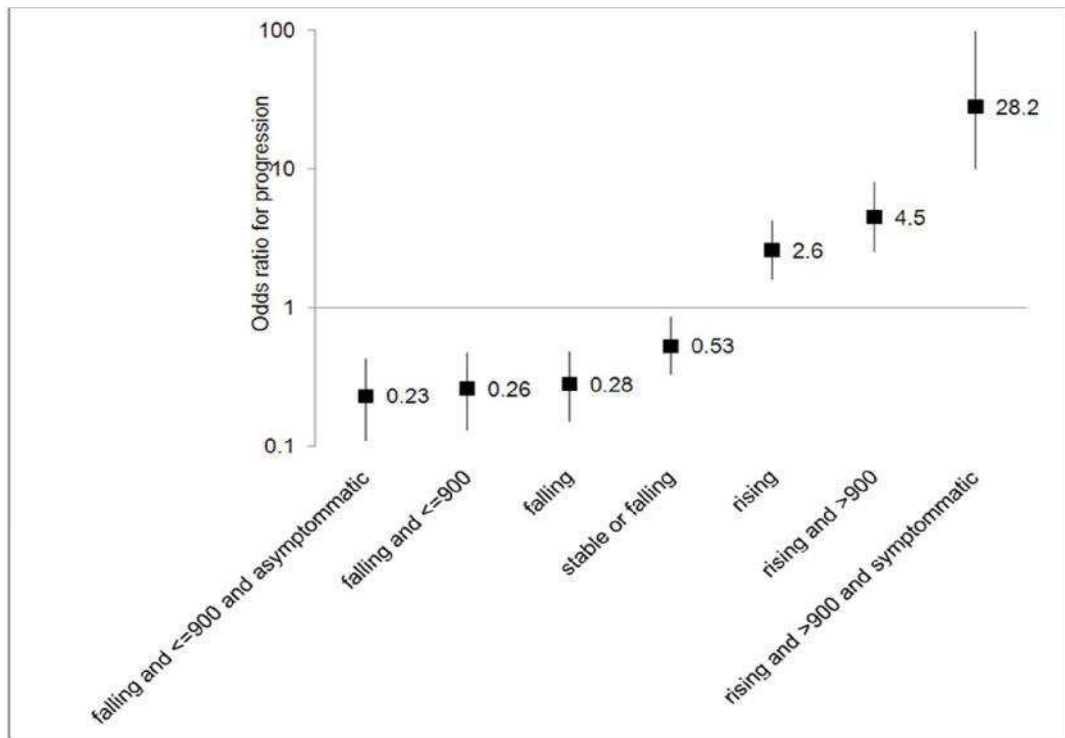


Figure 4b