Visualization of DAS28, SDAI and CDAI: the magic carpets of rheumatoid arthritis

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Visualization of DAS28, SDAI and CDAI: the magic carpets of rheumatoid arthritis

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Abstract

Objective. There has been continuous debate regarding the applicability of various composite measures for the assessment of disease activity in rheumatoid arthritis (RA). In order to further dissect this issue, we numerically and graphically modeled DAS28, SDAI and CDAI by 3-dimensional plotting. We wished to graphically visualize the relative contribution of various elements in the three activity indices to each other.

Methods. We calculated DAS28 (3-variable), SDAI and CDAI by the standard equations. We plotted 3-dimensional (3D) "carpets" showing all combinations of the corresponding variables yielding to DAS28=5.1, DAS28=3.2, DAS28=2.6, SDAI=26, SDAI=11 and SDAI=3.3. We also plotted the 3D carpet for CDAI.

Results: In patients with high or moderate disease activity, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) were not major confounding factors when calculating DAS28 and SDAI, respectively. In contrast, ESR and CRP highly overshadowed changes in joint counts and global assessments in patients with low disease activity (LDA) or in those in remission. No reliable assessment of LDA can be performed in cases where ESR>54 mm/h or CRP>20 mg/dl. Similarly, remission cannot be determined if ESR>19 mm/h or CRP>5 mg/dl. As CDAI does not include acute phase reactants, CDAI may be a useful tool even in states of remission or LDA.

Conclusions: Our results suggest that acute phase reactnats are indeed major confounding factors and should be omitted when assessing RA disease activity, at least in special cases.

Introduction

Rheumatoid arthritis (RA) is a progressive inflammatory rheumatic disease, which may lead to joint destruction and disability. Thus, early diagnosis, close follow-up and early, effective treatment are imperative in order to prevent structural damage and functional impairment (1, 2). Various instruments have been developed in order to accurately determine disease activity of RA at any given timepoint during the disease course (2). Among disease activity indices, the 28-joint disease activity scale (DAS28) has long been used in the daily practice, as well as in clinical trials. The 3-variable DAS28 (DAS28-V3) includes erythrocyte sedimentation rate (ESR), swollen (SJC) and tender joint counts (TJC) determined in 28 designated joints, while the 4-variable version (DAS28-V4) also includes patient-determined global health (GH) assessed on a 100-mm visual analogue scale (VAS) (2-4). However, the somewhat complicated formula requires the use of special calculators or computer softwares (Table 1). Therefore a simplified disease activity index (SDAI) has later been developed by simply adding five variables including SJC, TJC in 28 joints, C reactive protein level (CRP, mg/dL), as well as patient- (PGA) and evaluator-determined global disease activity (EGA) assessed by 10-cm VAS (5-7). Some further studies suggested that the determination of acute phase reactants (APR), such as ESR or CRP add little to the other four parameters when assessing SDAI (8). Therefore an even more simple clinical disease activity index (CDAI) has been introduced by omitting CRP and just adding the other four variables, SJC, TJC, PGA and EGA (5, 6, 9). The elements of these composite indices and the calculation formulas are included in Table 1.

It has become clear from routine clinical practice that the “APR issue” may have another important aspect. Apart from not giving extra value during the determination of disease activity (8), ESR and CRP may even overshadow the other clinical parameters. Indeed, APRs reflect systemic inflammation and, in most patients, reflect disease activity.

However, we often see patients with LDA of RA, yet highly elevated ESR or CRP levels due to other confounding factors, such as infections, paraproteins or simply high immunoglobulin or total protein levels. On the other hand, some patients may have highly destructive RA despite "low-grade" inflammation. In such conditions, very low or very high APR levels may override the influence of other clinical variables when determining DAS28 or SDAI. As very recently published by Smolen and Aletaha (10), the determination of response to biologics may be highly influenced by APRs as much better reponse to tocilizumab was observed using DAS28 in comparison to CDAI.

In order to further dissect this issue, we numerically and graphically modeled DAS28, SDAI and CDAI by 3-dimensional plotting. Our aim was to compare and graphically visualize the relative contribution of various elements in the three activity indices to each other. Our results suggest that APRs are indeed major confounding factors and should be omitted when assessing RA disease activity, at least in special cases.

Methods

DAS28-V3 graphs

We used the 3-variable version of DAS28. DAS28-V3 was calculated by using the standard equation of DAS28 = (0.56 x $\sqrt{\ }$ TJC + 0.28 x $\sqrt{\ }$ SJC + 0.7 x ln ESR) x 1.08 + 0.16. According to the definition of high, low disease activity and remission (Table 1), DAS28 = 5.1, 3.2 and 2.6, respectively, were calculated using all possible TJC (0-28), SJC (0-28) and ESR (0-100 mm/h) values. Then, three-dimensional (3D) graphs were plotted with TJC, ESR and SJC on the X, Y and Z axes, respectively, expressing DAS28 values of 5.1 (Figure

1a,B,C), 3.2 (Figure 2A,B,C) and 2.6 (Figure 3A,B,C). 3D "carpets" are presented as snapshots taken from different views.

SDAI graphs

SDAI was calculated by the standard equation of SDAI = TJC + SJC + PGA + EGA + CRP, assessing 28-jount counts (Table 1). As five variables cannot be plotted in 3D graphs, TJC and SJC were added yielding to a composite joint score (TJC+SJC: 0-56), PGA and EGA were also added yielding to a composite assessment score (PGA+EGA: 0-20) and these two composite scores were plotted against CRP. Now we ended up with only 3 variables. As the SDAI limits between high/moderate, moderate/LDA and LDA/remission are 26, 11 and 3.3, respectively (Table 1), we plotted three 3D graphs expressing SDAI values of 26 (Figure 4), 11 (Figure 5) and 3.3 (Figure 6). In these "carpets", TJC+SJC, CRP and PGA+EGA were plotted on the X, Y and Z axes, respectively.

CDAI graphs

CDAI was calculated by the standard formula of CDAI = TJC + SJC + PGA + EGA by assessing 28 joints (Table 1). As 4 variables cannot be plotted in 3D graphs and we also wished to compare SDAI and CDAI graphs, we, similarly to what was performed in the case of SDAI, we again formed two composite indices by adding TJC+SJC and also PGA+EGA. This yielded to only two variables so in this situation TJC+SJC and PGA+EGA were plotted on X and Z axis, and all CDAI values could be visualized in on the Y axis of 3D carpets (Figure 7A,B).

Results

The DAS28 carpets

In Figures 1, 2 and 3 carpets of DAS28=5.1, 3.2 and 2.6 are visualized as snapshots taken from three different views (A,B,C), respectively. The DAS28=5.1 carpet (Figure 1A-C) reflects all possibilities, how high disease activity can be presented. When looking at some examples, on one hand, taken the maximum SJC and TJC values of 28 each, ESR = 1.2 mm/h indicating that DAS28=5.1 can be reached if ESR is above 1 mm/h. In addition, patients with 0 or 1 tender and/or swollen joints would require ESR > 200 mm/h to reach DAS28=5.1, which is defitely not realistic. Thus, in the case of DAS28=5.1, ESR is not a major confounding factor.

When the carpet of DAS28=3.2 is plotted (Figure 2A-C), it is clear from the examples that zero TJC and SJC correspond with ESR=54 mm/h. Thus, patients with ESR > 54 mm/h may never reach LDA. As some patients may exert higher ESR despite of no or very few tender and swollen joints, ESR may be a confounding factor when calculating DAS28 and may override the weight of the other two variables.

Similarly, when the carpet of DAS28=2.6 is visualized (Figure 3A-C), zero TJC and SJC correspond with ESR=19 mm/h. Thus, RA patients with ESR>19 mm/h would never reach the state of remission.

The SDAI carpets

In Figures 4, 5 and 6, carpets of SDAI=26, SDAI=11 and SDAI=3.3 are visualized as snapshots, respectively. The SDAI=26 carpet (Figure 4) reflects all possibilities, how high

disease activity can be reached. If SJC+TJC or PGA+EGA sums are below 26, CRP is positive. In the case of cutoff between moderate and low disease activity (SDAI=11), most of the carpet is "on the floor", only TJC+SJC or PGA+EGA sums below 11 would yield positive CRP values (Figure 5). As for remission (SDAI=3.3), CRP must be 3.3 mg/dl or lower that yields to an almost flat graph. Both the TJC+SJC and the PGA+EGA sums must be <3, otherwise CRP would yield negative value (Figure 6). Thus, in the case of relatively high joint and/or assessment scores (>26), high disease activity can easily be reached, irrespective of CRP (Figure 4). In contrast, when the carpets of SDAI=11 and SDAI=3.3 are plotted (Figures 5 and 6), almost the whole carpet is "on the floor". In these cases, CRP cannot be more than 11 mg/dl or 3.3 mg/dl, respectively, otherwise CRP would be a confounding factor when calculating SDAI and may override the weight of the other four variables. In other words, patiernts with CRP>11 mg/dl or with CRP>3.3 mg/dl could never show SDAI-determined LDA or remission, respectively (Figure 5 and 6).

The CDAI carpets

In Figure 7 (A and B), CDAI values are plotted on the Y axis against composite joint (X axis) and assessment scores (Z axis) formed similarly to SDAI visualization. CDAI carpets are visualized as snapshots taken from two different views (A,B). CDAI does not include CRP or ESR and is a simple sum of SJC+TJC+EGA+PGA. Thus, the calculation of CDAI is solely based on joint scores, as well as patient's and doctor's general assessments. As seen in Figure 7, there is no "carpet-on-floor" area indicating that CDAI is closely and linearly related with either joint counts or general assessments. Therefore, moderate disease activity (CDAI≤22), low disease activity (CDAI≤10) or remission (CDAI≤2.8) can be calculated upon any combination of the four variables, independent of any other confounding factors. Indeed,

a mean variable value of 5.5, 2.5 and 0.7 or less are required to reach moderate, low disease activity or remission, respectively.

Discussion

There has been continuous debate regarding the comparison and practical use of three different disease activity composite indices, DAS28, SDAI and CDAI in RA. In 2005, Aletaha et al (8) proposed that APRs added little to composite indices. This led to the development of CDAI, an index not containing ESR or CRP (6, 11, 12).

As most published papers presented calculations, we wished to visualize the distribution of various components in the three composite indices by drawing 3-dimensional "carpets" and by also presenting some examples in tables.

Our data confirm that while APRs may be useful when calculating DAS28 or SDAI in RA patients with high or moderate disease activity, ESR and/or CRP may be confounders of these calculations in patients with low disease activity or in those in remission. When using DAS28, ESR values >54 mm/h and >19 mm/h or, similarly, when calculating SDAI, CRP values >11 mg/dl and >3.3 mg/dl make the respective determination of LDA and remission impossible. In contrast, CDAI carpets indicate very good correlations of RAQ disease activity with joint scores, as well as patient- and doctor-determined measures without the confounding effects of APRs.

Some groups have also suggested that composite indices, such as DAS28 or SDAI may exert problems when used in remission or in LDA states (12-15). It is imperative to use proper tools to assess remission and LDA, as nowadays, according to the recent EULAR and treat-to-target recommendations, standard care, as well as clinical trials should target these disease states (13, 16-19). Furthermore, remission has also been associated with radiographic

progression, especially in patients with residual joint swelling (20). Interestingly, as among biologics tocilizumab may have outstanding suppressive effects on APR production, APR-containing composite measures may be very sensitive tools in this special setting (15).

Very recently, Bentley et al (11) developed a modified version of DAS28 (mDAS28) that also lacks APRs. Modified DAS28 showed substantial agreement with DAS28, SDAI amd CDAI.

In conclusion, our visualization of RA disease-activity "carpets" confirm that ESR and/or CRP may be significant confounding factors when assessing patients in remission or those with LDA.

Figure legends

Figure 1. Variability of three components (erythrocyte sedimentation rate [ESR], tender [TJC] and swollen jount counts [SJC]) leading to DAS28=5.1 (borderline between high and moderate disease activity) shown as a 3-dimensional "carpet" from three viewpoints (1A,1B,1C).

Figure 2. Variability of three components (erythrocyte sedimentation rate [ESR], tender [TJC] and swollen jount counts [SJC]) leading to DAS28=3.2 (borderline between moderate and low disease activity) shown as a 3-dimensional "carpet" from three viewpoints (2A,2B,2C).

Figure 3. Variability of three components (erythrocyte sedimentation rate [ESR], tender [TJC] and swollen jount counts [SJC]) leading to DAS28=2.6 (borderline between low disease activity and remission) shown as a 3-dimensional "carpet" from three viewpoints (3A,3B,3C).

Figure 4. Variability of three components (C reactive protein [CRP], tender [TJC] + swollen jount counts [SJC], patient's [PGA] + doctor's global assessment [EGA]) leading to SDAI=26 (borderline between high and moderate disease activity) shown as a 3-dimensional "carpet".

Figure 5. Variability of three components (C reactive protein [CRP], tender [TJC] + swollen jount counts [SJC], patient's [PGA] + doctor's global assessment [EGA]) leading to SDAI=11 (borderline between moderate and low disease activity) shown as a 3-dimensional "carpet".

Figure 6. Variability of three components (C reactive protein [CRP], tender [TJC] + swollen jount counts [SJC], patient's [PGA] + doctor's global assessment [EGA]) leading to SDAI=3.3 (borderline between low disease activity and remission) shown as a 3-dimensional "carpet".

Figure 7. Variability of tender [TJC] + swollen jount counts [SJC], patient's [PGA] + doctor's global assessment [EGA] and CDAI shown as a 3-dimensional "carpet" from two viewpoints (7A,7B).

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None of the authors have any conflict of interest.

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Table 1 Calculation and interpretation of DAS28-V3, SDAI and CDAI

	Formula	High disease activity	Moderate disease activity	Low disease activity	Remission
DAS28-V3	(0.56 x $\sqrt{}$ TJC + 0.28 x $\sqrt{}$ SJC + 0.7 x ln ESR) x 1.08 + 0.16	>5.1	≤5.1	≤3.2	≤2.6
SDAI(28)	TJC + SJC + PGA + EGA + CRP	>26	≤26	≤11	≤3.3
CDAI(28)	TJC + SJC + PGA + EGA	>22	≤22	≤10	≤2.8

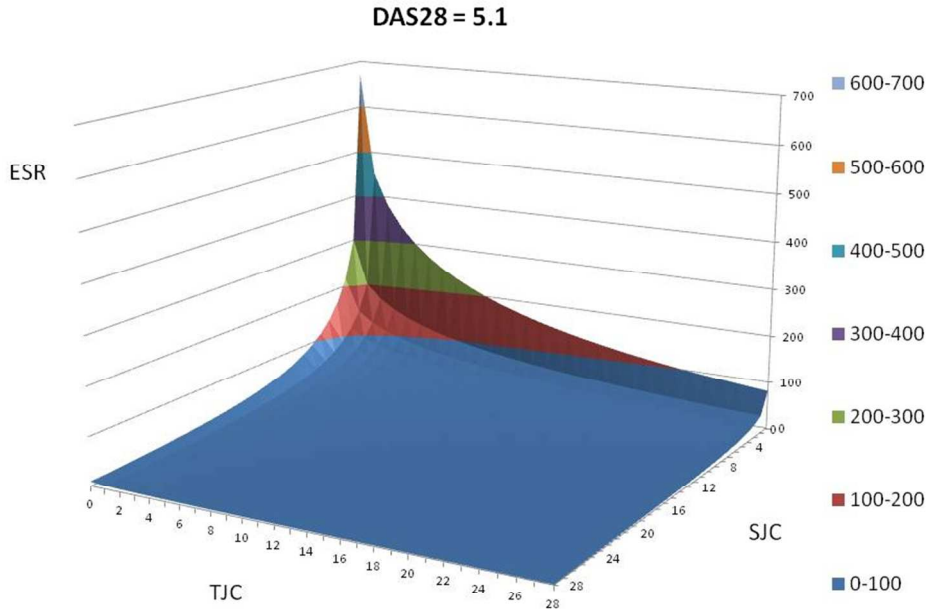

Figure 1A

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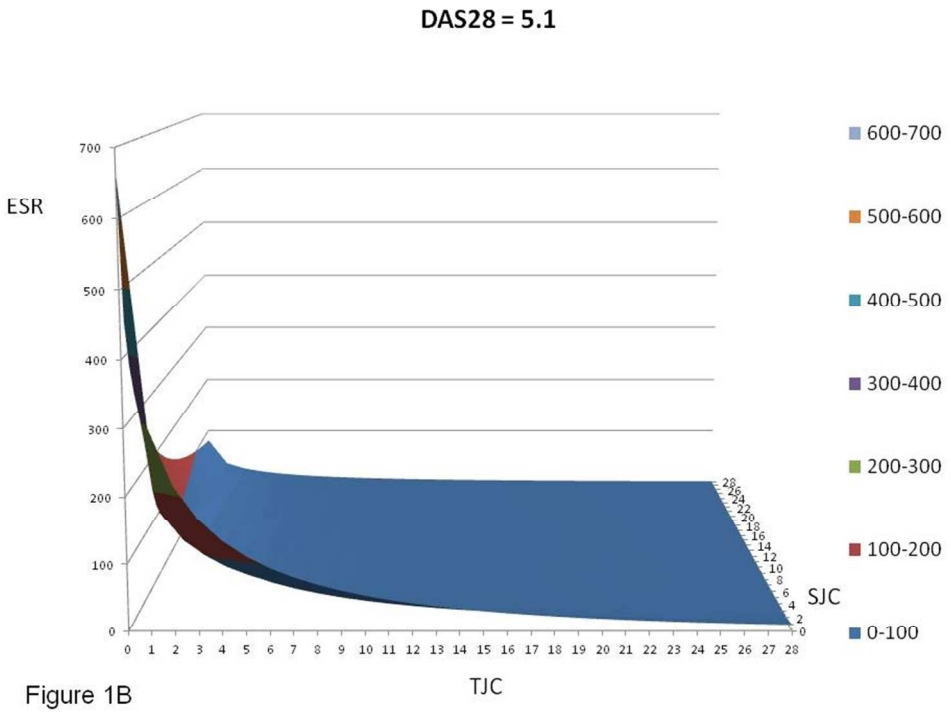

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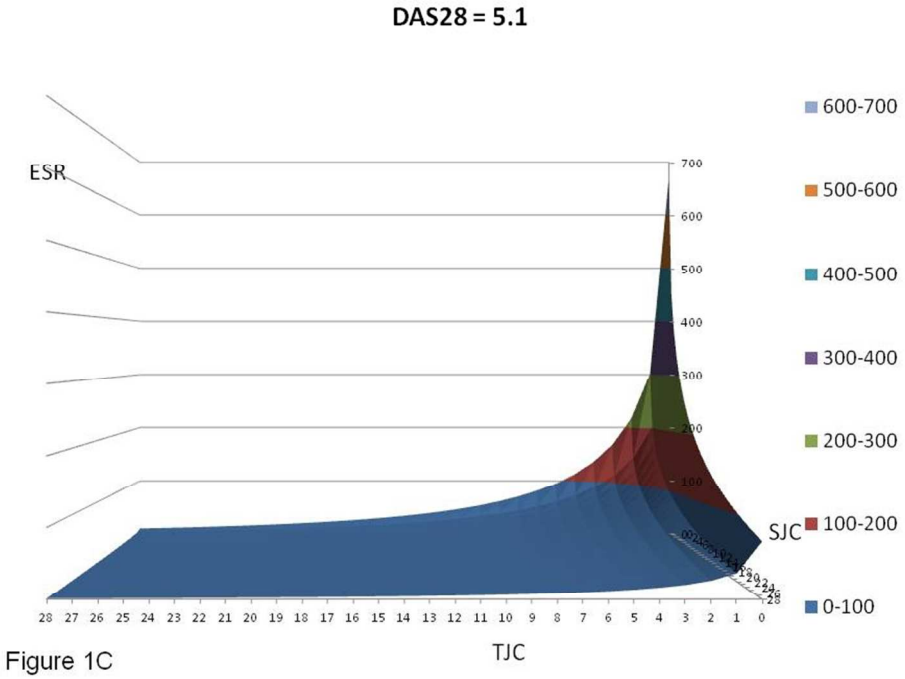

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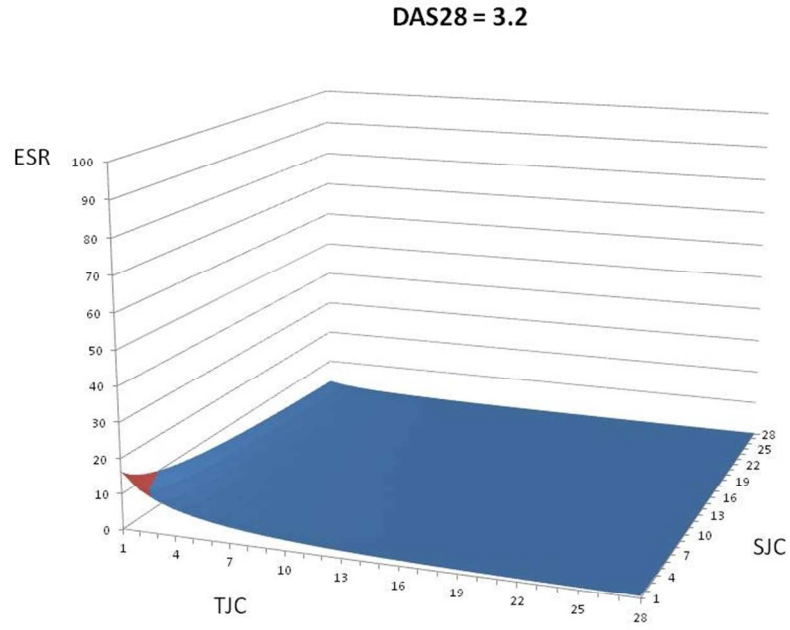

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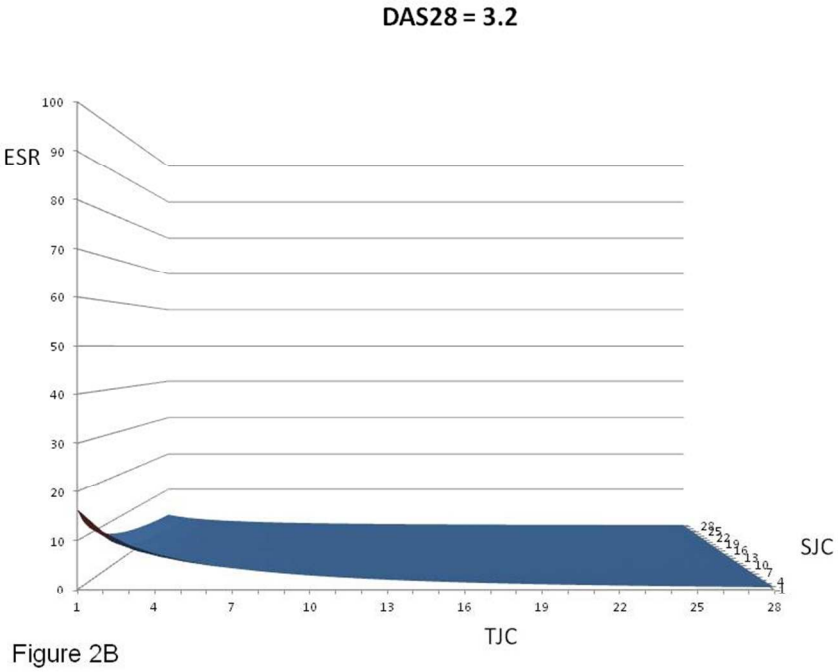

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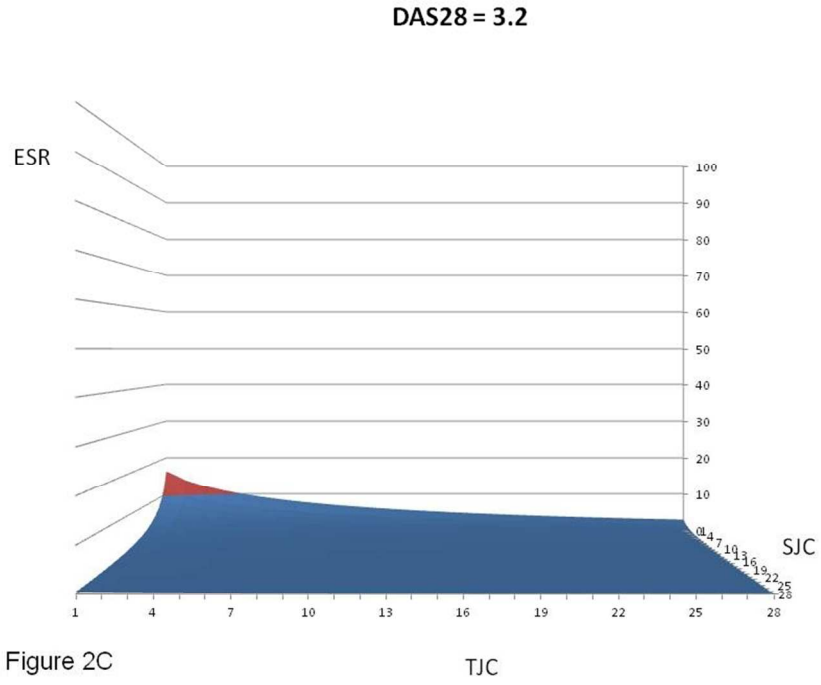

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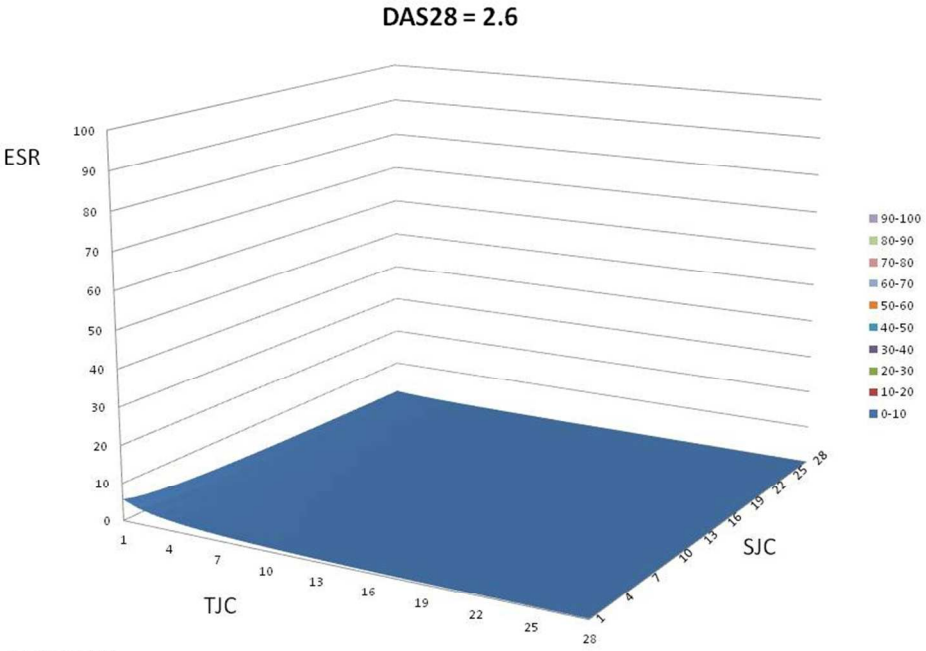

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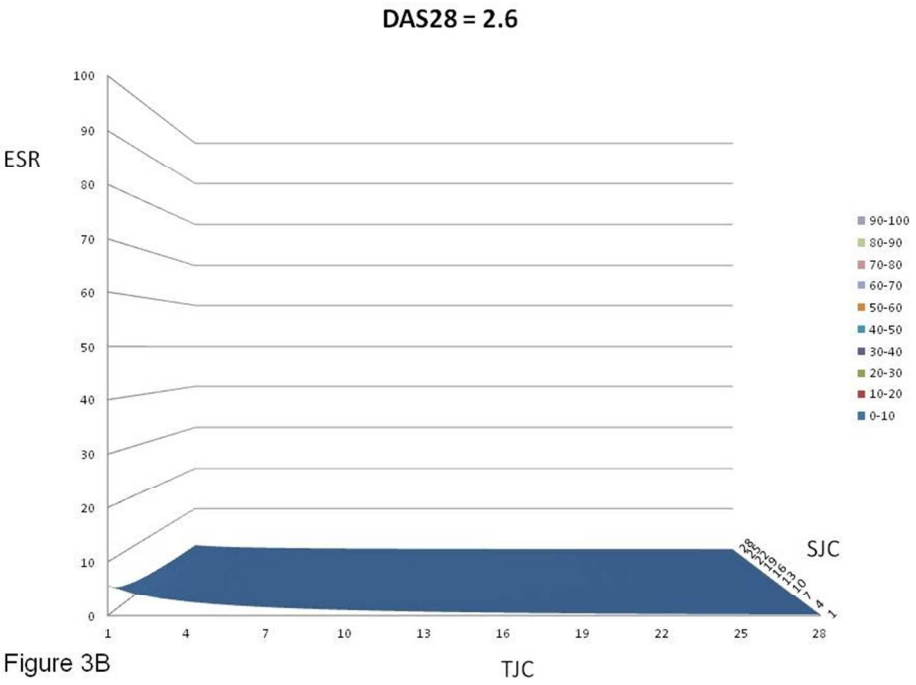

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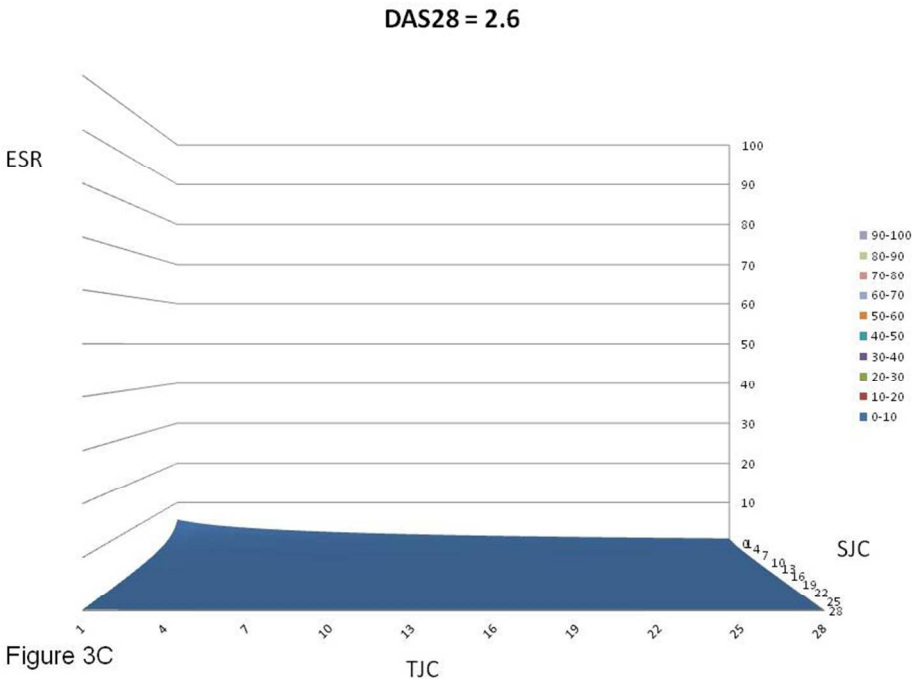

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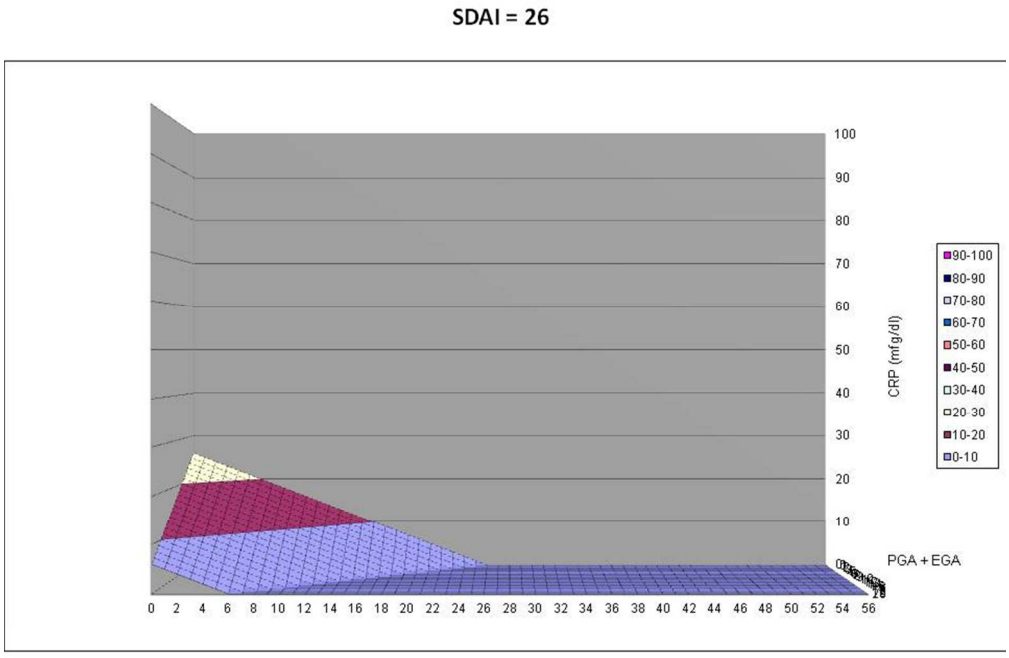

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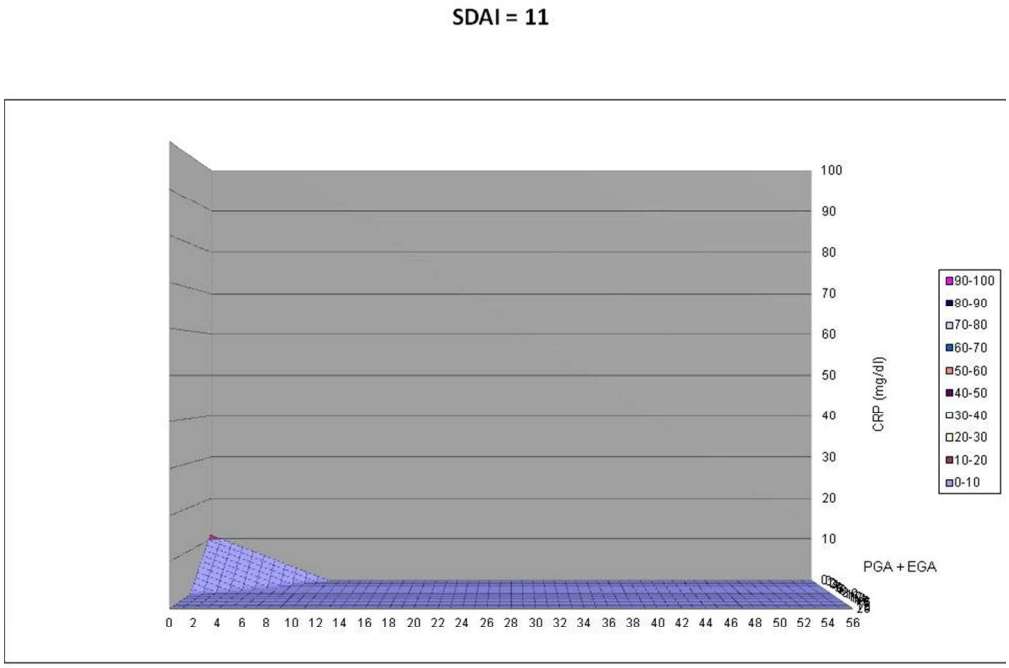

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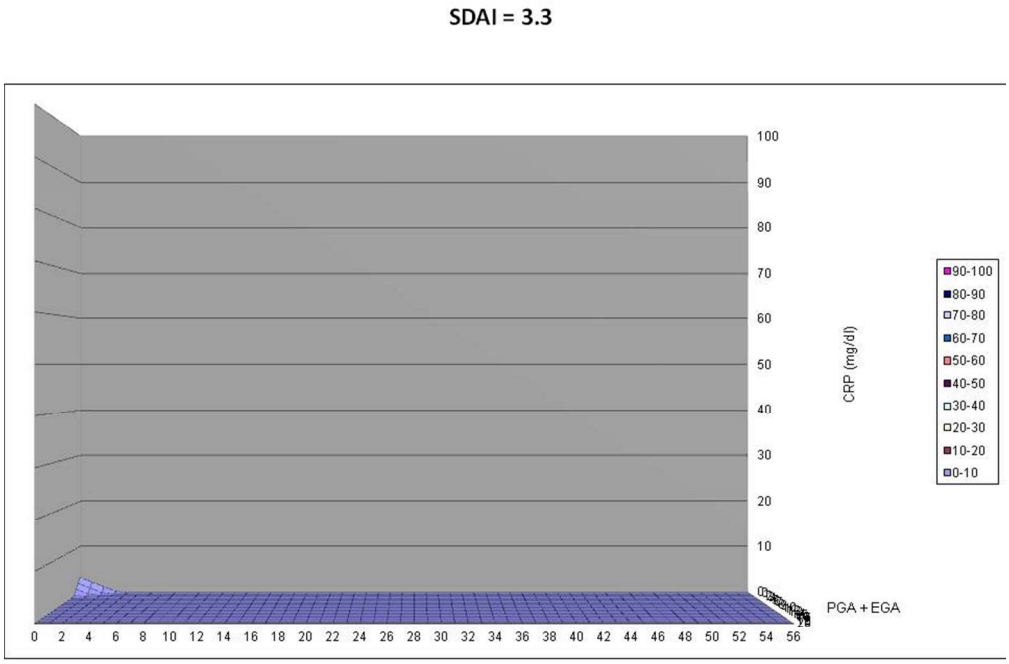

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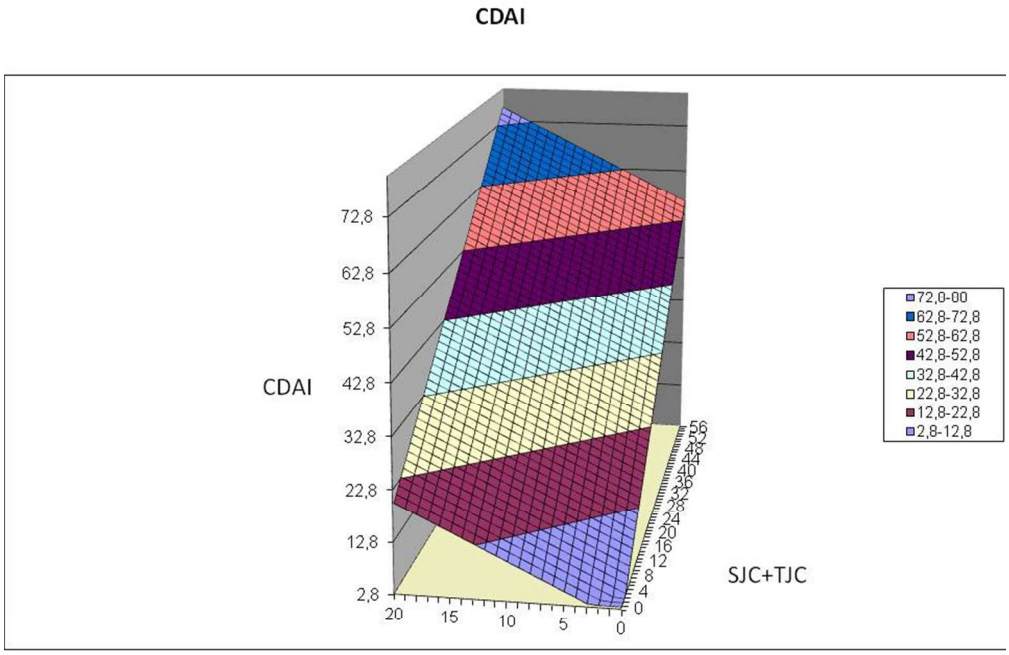

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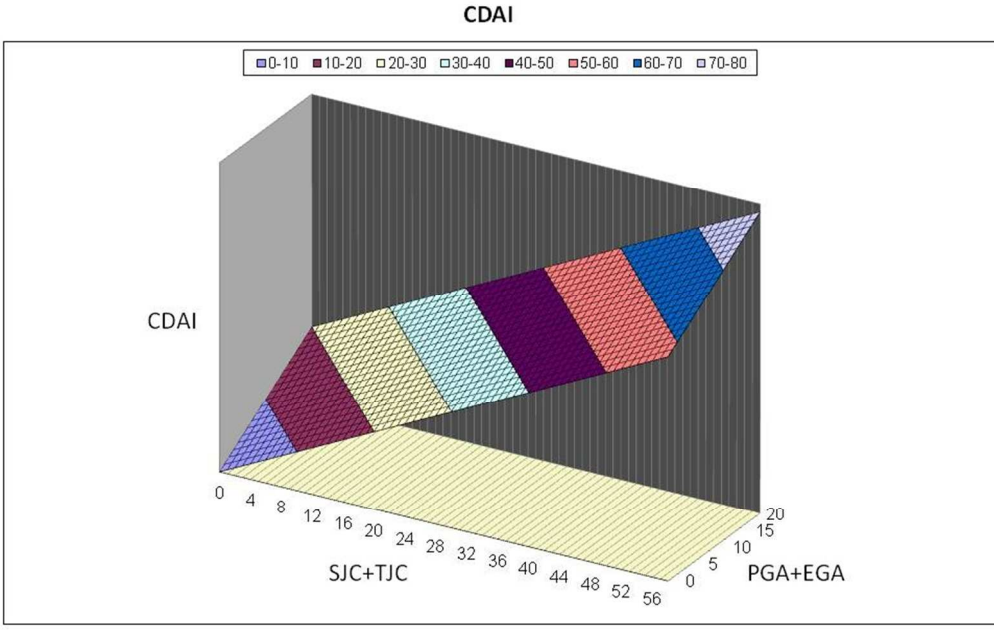

Figure 7B

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