Author’s response to reviews

Title: Atrophic inferior vena cava is a marker of chronicity of intra-filter and inferior vena cava thrombosis: based on CT findings

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Author’s response to reviews:

To the Editors and Reviewers:

Thank you very much for offering us this opportunity to revise the manuscript. We have revised it point by point in accordance with your comments. We hope the revised manuscript meets the acceptance standards of the BMC Cardiovascular Disorders. Please see below the responses to your comments and the revisions made.

-Salah Dine Qanadli (Reviewer 1)

The authors report a short experience (8 patients) of vena cava filter related-thrombosis. The topic is of interest and observations reported might bring several insights. However, I have several comments and concerns about the design and the methodology that could help the authors to improve messages for readers:
DESIGN:

(1) It is mandatory to clarify which population the authors are dealing with. It seems to me that patients were identified from CT scans done for several reasons. Thus, some patients were asymptomatic or all patients presented thrombosis related symptoms. Please better define the study design.

Reply: Thanks very much for your comments and helpful suggestions. We extracted these 8 patients from among 562 total patients with thrombosis simply because they had complete CT scans that revealed the progression of caval filter thrombosis from the acute to the chronic stage. Other patients may have had thrombosis in the filter, but the CT scans were incomplete, so we did not include them in the study.

The initial main symptoms of these patients included swelling of the diseased leg (n=8) and calf pain (n=6). After placing the filter, all patients had persistent swelling on the diseased leg and developed swelling of the contralateral leg. Three male patients reported moderate pelvic pain with scrotal swelling. Ascites was found in four other patients.

We added this information in the Methods section (in red font).

"These eight patients (among the 562 reviewed) were included in the study simply because they had a complete set of CT scans that revealed the progression of their intra-filter and IVC thromboses from the acute to the chronic stage. The other patients might have had intra-filter or IVC thrombosis but were excluded because of incomplete sets of CT scans." (p. 6, lines 8-12)

"The main initial symptoms of these patients included swelling on the affected leg (n=8) and calf pain (n=6). After filter placement, all patients had intermittent swelling of the affected leg and later developed swelling on the contralateral leg. Three male patients reported moderate pelvic pain with scrotal swelling. Ascites was found in four patients." (p. 7, lines 3-7)

(2) The study was focused on "Filter related thrombosis". In my opinion, there is a difference between "filter thrombosis" and "filter related thrombosis". The second one means
that the filter induces thrombosis, which is matter of debate but nothing is supporting this theory in the presented data.

Reply: Thanks very much for making the distinction between "filter thrombosis" and "filter-related thrombosis." What we wanted to express was caval thrombosis following filter placement, not the initial lower extremity DVT. To avoid any misunderstanding, we changed the term to "intra-filter and IVC thrombosis" instead of "filter related" thrombosis. Please see the changes in the text through the paper (including in the title and figure legends) (in red font).

(3) Optease and Trapease are basket shape based filters. Usual there is no penetration with this kind of filters. The observed penetration is only due to the vena cava retraction induced by post thrombotic remodeling. Introducing penetration with these filters needs to be clarified and discussed

Reply: Thanks very much for the helpful comment. We agree that basket-shaped filters are at less risk of penetration. We also think the term "protrusion" may be better and more objective than "penetration" to describe the phenomenon. Please see the changes in the text through the manuscript (include the title and figure legends) (in red font).

We also added a comment in the Discussion section.

"Moreover, the filters used in the study were basket-shaped filters. Usual there is no penetration with this kind of filter, but with post-thrombotic remodeling the IVC could retract, causing filter protrusion on CT imaging. For this reason, we did not use "penetration" to describe this possibility, but "protrusion." (p. 14, lines 9-13)

METHODS

(1) How patients were followed after filter insertion? Is there a systematic CT follow up? Is it possible to have some patients with filters not followed by CT?, and by the way some filters with occlusion not identified?
Reply: Thanks very much for the comment. In our center, the patients with DVT that
developed after filter insertion were commonly followed by ultrasonography or ascending
venography at 6-month intervals during the first year and once a year thereafter. CT-based
follow-up was not a conventional method because of concerns about radiation exposure and the
use of contrast media. Hence, some of the patients with filters were not followed by CT, and
some filters with occlusion were likely not identified, especially if silent or asymptomatic. The
use of CT is recommended in our center only if propagation of the thrombus or caval occlusion
is suspected.

We added the follow-up protocol in the Methods section (in red font).

"These patients had been followed by ultrasonography or ascending venography at half-year
intervals during the first year and then once a year thereafter. CT was required only if there was
thrombus propagation into the IVC or suspected intra-filter thrombosis." (p. 6, lines 1-4)

(2) No patient had pulmonary embolism. Filters were inserted to prevent PE in
patients with DVT. Why a short-term optional (or even permanent) filters are chosen in this
population? Probably long-term optional filters are more appropriate.

Reply: Thanks very much for the comments. For the eight patients included in the study,
the filter was placed because coagulation therapy was contraindicated, and they was had
proximal thromboses. We agree that long-term optional filters are more appropriate because they
can provide relatively longer protection and allow a longer time frame for removal if required.

The patients included in the study were all treated before 2015. At that time, only a short-
term option (e.g., OptEase) or permanent filters (e.g., TrapEase, Simmon) were commercially
available in China. Only in recent years (since 2016) has a long-term filter (e.g., Celect) become
an option here. Even today, Option and Denali filters are seldom used in some large centers in
China.

We have added a comment in the Discussion (in red font).
"All eight of the patients in this study were treated with basket-shaped filters, which are associated with a higher risk of intra-filter thrombosis than are conical filters [17]. For patients who require long-term protection against a pulmonary embolism, a long-term optional filter (e.g., Celect, Option, Denali) might be more appropriate. Moreover, if available, the preferred filter is one that could be retrieved via jugular access in case of a proximal DVT." (p. 13, lines 19-21 – p. 14, lines 1-3)

Correspondingly, we added Reference 17 to the list.


(3) No information was provided regarding patients symptoms, particularly regarding the new onset (filter thrombosis).

Reply: Thanks very much for the comment. We added this information in the text as follows (in red font).

"These eight patients (among the 562 reviewed) were included in the study simply because they had a complete set of CT scans that revealed the progression of their intra-filter and IVC thromboses from the acute to the chronic stage. The other patients might have had intra-filter or IVC thrombosis but were excluded because of incomplete sets of CT scans." (p. 6, lines 8-12)

"The main initial symptoms of these patients included swelling on the affected leg (n=8) and calf pain (n=6). After filter placement, all patients had intermittent swelling of the affected leg and later developed swelling of the contralateral leg. Three male patients reported moderate pelvic pain with scrotal swelling. Ascites was found in four patients." (p. 7, lines 3-7)
No information was provided regarding the DVT location (proximal, distal, iliac, femoral…). This might help understand the potential relationship between DVT and filter thrombosis.

Reply: Thanks very much for the comment. We agree that the location of DVT is potentially associated with an intra-filter thrombosis. The intra-filter thromboses in the study were truly associated with proximal DVTs, including three involving the iliac veins only, three involving the iliac and femoral veins, and the other two involving the iliac or the femoral and popliteal veins.

We added this information in the text (in red font).

"All DVTs involved iliac veins. Three of the eight patients had additional involvement of the proximal femoral vein, and two had additional involvement of the femoral and popliteal veins, respectively." (p. 6, lines 14-16)

No information was provided regarding technical success of the filter placement. Is there any relationship between filter malposition and thrombosis.

Reply: Thanks very much for the comments. We added further information in the text (in red font).

"The technical success of filter placement was 100% (8/8) with no filter tilting or migration observed on venography immediately after filter placement. (p. 7, lines 13-15)

Seven of the filter with thrombosis were inserted from the left side. This observation should be discussed. Usually, more filter tilt is observed from the left in comparison to from the right side.

Reply: Thanks very much for the comments. We are sorry that incomplete information caused misunderstanding. We mentioned seven of eight patients had left-sided thrombosis
initially, for whom we placed filters via the right femoral vein. Only one filter was placed via the right side due to a left DVT. We also agree that more filter tilt is observed from the left.

We added this information in the text (in red font).

"Seven filters were placed in the IVC via the right femoral vein because of a left-sided DVT. Only one filter was placed via the left side because of a right-sided DVT." (p. 7, lines 11-13)

(7) In case of proximal DVT, the preferred filter to be inserted is the one that could be retrieved from the jugular access. Why the authors choose a filter that could be removed only from the femoral access?

Reply: Thanks very much for the comments. We agree that the preferred filter to be inserted is the one that could be retrieved via jugular access in case of a proximal DVT. However, the patients included in the study were all treated before 2015. At that time, a filter that could be retrieved from the jugular access was rarely available in China. Only in recent years (since 2016) has a filter that could be retrieved via jugular access (e.g., Celect) become available for use in China. Even today, Option and Denali filters are seldom used in some large centers in China.

We added a comment in the Discussion (in red font).

"Moreover, if available, the preferred filter is one that could be retrieved via jugular access in case of a proximal DVT." (p. 14, lines 2-3)

-Dalibor Musil (Reviewer 2):

According to the 9th ACCP guidelines in patients with acute proximal DVT/PE and contraindication to anticoagulation, the use of IVC filter (Grade 1B) is recommended. In some cases caval thrombosis is serious side effect. CT/CTV examination is diagnostic method of first choice. Authors try to establish the role of CT in the diagnosis of IVC filter-related thrombosis. In the retrospective study 8 patients undergoing an IVC filter placement for acute DVT of the
leg, developed acute filter-related thrombosis. In all cases it was DVT provoked by underlying serious disease.

Please answer the following questions:

1. Authors originally retrospective evaluated a group of 562 patients undergoing IVC filter placement, of which only 8 patients developed IVC filter-related thrombosis and were included into this study. Was IVC filter in other 554 patients removed or they didn’t develope any thrombosis?

   Reply: Thanks very much for your comments. We extracted these 8 patients from among 562 patients simply because they had complete CT scans that revealed progression of caval filter thrombosis from the acute to the chronic stage. The other patients may have had intra-filter thromboses, but their CT scans were incomplete. Also, not all of the other 554 patients underwent filter removal. In our center, approximately 80% of patients with filters undergo their removal if protection of the filter becomes unnecessary.

   We added following information to the text (in red font). (p6)

   "These eight patients (among the 562 reviewed) were included in the study simply because they had a complete set of CT scans that revealed the progression of their intra-filter and IVC thromboses from the acute to the chronic stage. The other patients might have had intra-filter or IVC thrombosis but were excluded because of incomplete sets of CT scans." (p. 6, lines 8-12)

   Not all patients with filter placement in our center required follow-up with CT. The patients with DVT after filter insertion are commonly followed using ultrasonography or ascending venography at half-year intervals during the first year and once a year thereafter. CT-based follow-up is not a conventional method due to concerns about radiation exposure and the use of contrast media. Hence, some patients with filters in this study were not followed using CT, and some occluded filters were likely not identified, especially if asymptomatic. The use of CT is recommended in our center only if propagation of the thrombus or caval occlusion is suspected.
We added our follow-up protocol to the Methods section (in red font).

"These patients had been followed by ultrasonography or ascending venography at half-year intervals during the first year and then once a year thereafter. CT was required only if there was thrombus propagation into the IVC or suspected intra-filter thrombosis." (p. 6, lines 1-4)

2. Which venous segments were primary involved, especially in the two survivors?

Reply: Thanks very much for the comment. In fact, all eight patients had a proximal DVT initially, including three in the iliac veins only, three in the iliac and proximal femoral veins, and one each also in the iliac, femoral, and popliteal veins.

We added this information in the text (in red font).

" All DVTs involved iliac veins. Three of the eight patients had additional involvement of the proximal femoral vein, and two had additional involvement of the femoral and popliteal veins, respectively." (p. 6, lines 14-16)

3. Why in CT study only 90 patients and in CTV study only 80 patients were involved (not 562)?

4. How many CT or CTV examinations were performed during the follow-up for each patient? What were the clinical indications for serialized CT/CTV scans at 8 followed patients - routine IVC filter follow-up, thrombosis related signs/symptoms or another cause (table 2)?

Reply: Thanks very much for the comments and helpful suggestions. Because these two questions are both about the CT studies, we will answer them together.

In the text (p. XX), we said:

"The most common study type was CT of the abdomen or abdomen/pelvis (68 of 90; 75.6%), followed by IVC-CTV (12 of 90, 13.3%), CT of the lumbar spine (six of 90, 6.7%) and of abdominal aorta (four of 90, 4.4%). Intravenous contrast-enhanced examinations accounted for 59 of the 80 total CT examinations (74%)."
We are sorry that we did not make it clearer. The numbers 68, 90, and 59 were not the number of patients undergoing CT examinations but the total number of CT examinations for the eight patients in the study.

CT was not used as a routine tool for DVT follow-up, as already discussed. Therefore, why did these eight patients undergo so many CT scans? First, they all underwent CT examinations to confirm the presence of an intra-filter and/or IVC thrombosis. During follow-up, two young patients with traumatic intracranial bleeding also underwent CT examinations. With regard to other patients, CT scans were performed for various reasons (e.g., tumor diagnosis and evaluation, bone pain, ascites). Thus, overall, there were 90 CT examinations (including plain and enhanced scans) for the eight patients, including 68 abdominal and pelvic CT scans and 12 IVC-CTV scans, among other miscellaneous scans. (Incidentally, "80" was a spelling error—it should have been "90".)

We revised this information in the text as shown below (in red font).

"Because CT studies were obtained for various clinical indications, there was considerable variability in the study type, the use of contrast agent, and the phase of contrast opacification of the vasculature. All eight patients underwent the first CT examination for a definitive diagnosis of intra-filter and IVC thrombosis. During the follow-up period, two young patients with traumatic intracranial bleeding underwent another CT examination. CT scans were performed in some other patients for various reasons, such as to evaluate the therapeutic response of a tumor, for bone pain, or for ascites, as well as to assess the filter and/or the thrombosis. Overall, the eight patients underwent a total of 90 CT examinations. The most common studies included CT of the abdomen or abdomen/pelvis (68/90, 75.6%), IVC-CTV studies (12/90, 13.3%), CT of the lumbar spine (6/90, 6.7%), and CT of the abdominal aorta (4/90, 4.4%)." (p. 7, lines 20-21 – p. 8, lines 1-9)

In addition, the sentence "Intravenous contrast-enhanced examinations accounted for 59 of the 90 total CT examinations (65.6%)" seemed unrelated to the topic, so we deleted it.
4. Caval thrombosis occurred very early after filter insertion (6-18 days). How the thrombosis was diagnosed, accidentally or based on some clinical signs or symptoms of recurrent DVT? It is reported that none of patients suffered from PE.

   Reply: Thanks very much for the comments. The intrafilter thrombosis in each of the eight patients was not diagnosed accidentally but based on clinical signs suggesting recurrent DVT or propagation of DVT. As the filter had been already placed, none of patients suffered from PE.

   We added this information in the text as follows (in red font).

   "However, DVT-related symptoms (e.g., swelling, pain) were not relieved, and new onset of contralateral leg swelling was observed, requiring further CT examination for a diagnosis." (p. 9, lines 9-11)

6. What was the interval between the filter insertion, filter penetration and secondary IVC atrophy? It is only reported that "the median interval between filter insertion and IVC agenesis was 8.62±1.41 months". IVC agenesis is not the correct term.

   Reply: Thanks very much for the comments. It is difficult to determine the precise intervals between filter insertion, penetration, and secondary IVC atrophy because the process of filter penetration and IVC atrophy occurs slowly and gradually. What we can determine is the interval between filter insertion and when filter penetration/secondary IVC atrophy was first revealed on CT. This information is available in Table 2 and in the text (in red font),

   "The median interval between filter insertion and protrusion first revealed on CT was 4.5±2.3 months (range 2–8 months)." (p. 10, lines 10-12)

   We agree that IVC agenesis is not the correct term, so we used the term "IVC atrophy" instead. (see p. 10, line 19).
7. Fibroid strip along the original track of IVC below the filter means that filter was eventually placed out of the atrophic IVC?

Reply: Thanks very much for the comment. The fibroid strip along the original track of the IVC below the filter did not mean that the filter was outside the atrophic IVC. The filter moving out of the IVC, as seen on CT, might be due to vena cava retraction induced by post-thrombotic remodeling. The filters used in the study were all basket-shaped, which provides less chance of being penetrated. To address this question, we think perhaps the term "protrusion" would be more descriptive than "penetration" to describe the phenomenon. Please see the changes in the text throughout the manuscript (including title and figure legends) (in red font).

And we added a comment in the Discussion.

"Moreover, the filters used in the study were basket-shaped filters. Usually, there is no penetration with this kind of filter, but with post-thrombotic remodeling the IVC could retract, causing filter protrusion on CT imaging. For this reason, we did not use "penetration" to describe this possibility, but "protrusion." (p. 14, lines 7-11)

To the Reviewers: Thank you again for your reviews and helpful suggestions. We hope that our responses have addressed your concerns. Please let us know if you require further clarification.

"The authors' response letter has been included as a supplementary file"